EXHIBIT F

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Guidance for Industry[1] Drug-Induced Liver Injury: Premarketing Clinical Evaluation

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I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug[2] to cause ***severe*** liver injury (i.e., fatal, or requiring liver transplantation). In particular, the guidance addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development. This evaluation is important because most drugs that cause severe DILI do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug will not show any cases. Databases do, however, often show evidence of a drug's *potential* for severe DILI if the clinical and laboratory data are properly evaluated for evidence of lesser injury that may not be severe, but may predict the ability to cause more severe injuries. This guidance describes an approach that can be used to distinguish signals of DILI that identify drugs likely to cause significant hepatotoxicity from signals that do not suggest such a potential. This guidance does not address issues of preclinical evaluation for potential DILI, nor the detection and assessment of DILI after drug approval and marketing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Gastroenterology Products, the Office of Medical Policy, and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] This guidance uses the term *drug* or *product* to refer to all products, except whole blood and blood components, regulated by CDER and CBER, including vaccines, and uses the term *approval* to refer to both drug approval and biologic licensure.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND: HEPATOTOXICITY

Hepatotoxicity has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Hepatotoxicity discovered after approval for marketing also has limited the use of many drugs, including isoniazid, labetalol, trovafloxacin, tolcapone, and felbamate (Temple 2001). Several drugs have not been approved in the United States because European marketing experience revealed their hepatotoxicity (e.g., ibufenac, perhexiline, alpidem). Finally, some drugs were not approved in the United States because premarketing experience provided evidence of potential toxicity (e.g., dilevalol, tasosartan, ximelagatran). Although most significant hepatotoxins have caused predominantly hepatocellular injury, indicated by leakage of aminotransferase (AT) enzymes from injured liver cells without prominent evidence of hepatobiliary obstruction, the pattern of injury can vary. Many drugs cause cholestasis, but in general this condition is reversible after administration of the offending drug has stopped. Cholestatic injuries are less likely to lead to death or transplant, although there have been exceptions.

Drugs cause liver injuries by many different mechanisms. These injuries resemble almost all known liver diseases and there are no pathognomonic findings, even upon liver biopsy, that make diagnosis of DILI certain. Therefore, when possible DILI is suspected, it is essential to gather additional clinical and laboratory information, to observe the time course of the injury, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, or C, autoimmune or alcoholic hepatitis, biliary tract disorders, and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy. It is also prudent to assess the subject for previously existing liver disease, such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to the experimental drug.

Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). Overtly hepatotoxic agents (e.g., carbon tetrachloride, chloroform, methylene chloride) are toxic to anyone receiving a large enough dose, and drugs that cause such predictable and dose-related injury generally are discovered and rejected in preclinical testing. More difficult to detect is toxicity that is not predictable or clearly dose-related, but seems to depend on individual susceptibilities that have, to date, not been characterized. Most of the drugs withdrawn from the market for hepatotoxicity have had rates of death or transplantation in the range of ≤ 1 per 10,000, so that a single case of such an event would not be reliably found even if several thousand subjects were studied. Cases of severe DILI have rarely been seen in drug development programs of significantly hepatotoxic drugs.

What are regularly seen during drug development are mild liver injuries, often laboratory signals without any symptoms. The problem is that both drugs capable of severe DILI and drugs that

have a low potential for causing severe injury (e.g., aspirin, tacrine, heparin, hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (*statins*)) can generate these types of signals. Therefore, an approach is needed that can distinguish drugs likely to cause severe DILI from drugs unlikely to do so.

In general, the type of liver injury that leads to severe DILI is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in serum AT activities reflecting release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug's potential for severe DILI. Many drugs that cause transient rises in serum AT activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that cause hepatocellular injury extensive enough to affect the liver's functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. It is important to identify those drugs as rapidly as possible.

The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals, generally have not shown dose-related toxicity, and, as noted, generally have caused low rates of severe injury in humans (1 in 5,000 to 10,000 or less). These reactions thus appear to reflect host factors and individual susceptibility. Consequently, they have been termed *idiosyncratic*, meaning dependent upon the individual person's particular constitution. Whether they are the result of genetic or acquired differences has not yet been established, and to date no genetic, metabolic, or other characteristic has been found to predict severe DILI in an individual.

Some severe DILI examples have been different from the more commonly seen hepatocellular idiosyncratic type. Perhexiline, an anti-anginal drug marketed in Europe, produced toxicity within months that had the histological appearance of alcoholic cirrhosis (Pessayre and Biachara et al. 1979). Fialuridine caused modest acute liver injury, but most strikingly led to severe metabolic acidosis and multiorgan failure as mitochondrial oxidative capacity was obliterated over a period of months (Kleiner and Gaffey et al. 1997; Semino-Mora and Leon-Monzon et al. 1997). Valproic acid causes hyperammonemic encephalopathy even without notable rises in serum AT activities. Benoxaprofen (Oraflex) induced intrahepatic cholestasis that over many months led to significant, sometimes fatal, liver injury, especially in elderly patients (Taggart and Alderdice 1982).

Retrospective evaluation of earlier experiences, augmented by recent experience, lead us to believe that appropriate testing and analysis in premarketing studies may improve the early detection of drugs that can cause severe hepatocellular injury.

III. SIGNALS OF DILI AND HY'S LAW

Because hepatocellular injury (AT elevations) is caused both by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, HMG-CoA reductase inhibitors, heparin) and drugs that do cause such injury, evidence of hepatocellular injury is a necessary, but not sufficient, indicator of a potential for severe DILI. The frequency of AT elevation is not a good indicator either, as drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of

patients. The degree of AT elevation may be a better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function.

As noted, a typical NDA or BLA database usually will not show any cases of severe DILI, even for a drug that can cause such injury. Many drugs, however, including both significant hepatotoxins and drugs that do not cause severe liver injury, cause laboratory evidence of hepatic injury, with leakage of liver enzymes and the appearance in blood of elevations in serum AT to levels of 3-, 5-, and greater times the upper limits of normal (ULN). Generally, ALT is considered a more liver-specific aminotransferase than AST, although it also occurs in many tissues (Green and Flamm 2002). The finding of a higher rate of such elevations in drug-treated subjects than in a control group is a sensitive signal of a potential to cause severe DILI, but it is not a very specific signal. A more specific signal of such potential is a higher rate of more marked peak AT elevations (10x-, 15xULN), with cases of increases >1,000 U/L causing increased concern. The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, however, is evidence of reduced overall liver *function* in one or more subjects, manifested by increased serum total bilirubin (TBL), in conjunction with AT elevation, not explained by any other cause, together with an increased rate of AT elevation in the overall study population compared to control.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). The reason for this now seems clear. The liver has a large excess of bilirubin-excreting capacity; injury to hepatocytes sufficient to cause jaundice or near jaundice (i.e., a bilirubin >2 mg/dL) represents an extent of damage so great that recovery may not be possible in some patients. Zimmerman's observation that hepatocellular injury sufficient to impair bilirubin excretion was ominous has been used at the Food and Drug Administration (FDA) over the years to identify drugs likely to be capable of causing severe liver injury, as distinct from drugs that cause lesser hepatocellular injury (i.e., AT elevation without bilirubin elevation) but are not as likely to cause severe injury (e.g., aspirin, tacrine, heparin). The observation of the critical importance of altered liver function has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004).

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

Finding one Hy's Law case in clinical trials is ominous; finding two is highly predictive of a potential for severe DILI. Clinical trials of the beta blocker dilevalol (enantiomer of labetalol, a diastereoisomeric mixture), showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. The manufacturer was asked to do a large-scale safety study before the drug could be approved. The study was never conducted.

As a rule of thumb, based on Zimmerman's original estimate of 10 to 50 percent mortality associated with hepatocellular injury sufficient to impair the liver bilirubin excretory function, severe DILI can be estimated to occur at a rate of at least one-tenth the rate of so-called Hy's Law cases (Temple 2001). This observation was recently confirmed in large studies of DILI in Spain (Andrade and Lucena et al. 2005) and in Sweden (Björnsson and Olsson 2005) in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants.

Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing. These examples are described in detail in Appendix A.

Past experience, including the three examples, shows that there is a set of laboratory abnormality signals that have the ability to predict a potential for severe DILI with reasonable sensitivity and specificity in a database of several thousand subjects. Although it is not yet possible to provide precise specificity and sensitivity estimates for the various signals, guidance can be provided on use of these major indicators of a potential for severe DILI, as follows:

- **An excess of AT elevations to >3xULN compared to a control group**

  AT elevations to >3xULN are relatively common and may be seen in all groups, but an excess of these elevations compared to a control group is nearly always seen for drugs that ultimately prove severely hepatotoxic at relatively high rates (1/10,000). Therefore, the sensitivity of an excess of >3xULN AT elevations as a predictor of a potential for severe DILI is high. But many drugs show this signal without conferring a risk of severe injury (e.g., tacrine, statins, aspirin, heparin), indicating low specificity for an excess of AT elevations alone. There are no good data analyses at this time on how great this excess should be compared to control (e.g., 2-fold, 3-fold) to suggest an increased risk of DILI.

- **Marked elevations of AT to 5x-, 10x-, or 20xULN in smaller numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group**

  Virtually all severely hepatotoxic drugs show such cases, indicating high sensitivity for predicting severe DILI, but, again, some drugs such as tacrine and others that are not severely hepatotoxic also can cause AT elevations to this degree, so that specificity of this finding is suboptimal.

- **One or more cases of elevated bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP in gall bladder or bile duct disease, malignancy), with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs), accompanied by an overall increased rate of AT elevations >3xULN in the test drug group compared to placebo**

  The sensitivity of this observation appears high for any given rate of severe DILI if enough people are exposed to the drug. Thus, if the true incidence of severe injury is 1/10,000, and the rate of Hy's Law cases is 1/1,000, about 3,000 subjects (*Rule of 3*) would be needed to have a 95 percent probability of observing a Hy's Law case in the treated population (Rosner 1995). The sensitivity of this finding appears very high if at least two cases are seen (e.g., dilevalol, bromfenac, troglitazone, ximelagatran). We are not aware of false positive Hy's Law findings. Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant rate of severe liver injury. Failure to find a case, however, does not imply that a drug with AT elevations is free of a risk of severe DILI. The degree of assurance depends on the population exposed for a long enough time and on the rate of severe DILI that would be of interest.

The implications of these three findings may be different in patients with existing liver disease such as fatty liver disease, NASH, or chronic hepatitis C or B, with bilirubin metabolism abnormalities (Gilbert's syndrome), and in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).

IV. CLINICAL EVALUATION OF DILI

A. General Considerations

For most drugs in development that reach phase 3 testing, the chances of encountering severe DILI are low. An increased frequency of mild hepatotoxicity (AT elevations) in early trials usually results in heightened screening to detect and evaluate liver injury during phase 3 testing. It is critical, however, to determine whether mild hepatotoxicity reflects a potential for severe DILI or reflects a capacity for only limited injury. To make this distinction, it is essential to detect any cases of more severe injury and to examine such cases closely, observing the course and outcome of the injury, and seeking additional information that might identify other causes. The following general recommendations for evaluating and monitoring potential drug-induced hepatotoxicity may not be suitable for all situations and should be modified for special populations, such as people with preexisting liver disease or malignancies, and in light of accumulating data. In addition, clinical trials of cellular and gene therapies and of vaccines pose specific challenges related to trial size and design, persistence of vectors, and tissue specificity. Applicants are encouraged to discuss these issues with the review division.

1. Patients with Liver Abnormalities or Disease

Patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, except perhaps to avoid confusion between the previous disease and an effect of the test drug. These patients generally should be included in at least the phase 3 trials because they are likely to be treated with the drug if it is marketed. Preexisting liver disease is not known to make patients more susceptible to DILI (Zimmerman 1978, 1999), but it may be that a diminished *liver reserve* or the ability to recover could make the consequences of injury worse, making it appear that such patients were more susceptible to severe DILI. If the drug is intended to be prescribed or marketed to such patients after approval, they should be studied during controlled trials. It may be prudent, however, to first determine if DILI occurs in people with previously normal livers, before studying patients with well-characterized and stable chronic liver disease.

2. Detection of DILI

In general, early studies of a drug in study subjects with presumably normal liver function should involve obtaining liver tests every 2 to 4 weeks, at least for a few months. It is uncertain whether early symptoms (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting) precede or follow the first laboratory signs of hepatic injury (rising ALT, AST, or ALP) and the pattern of clinical and laboratory changes may vary with different drugs and recipients. In most cases, however, the first evidence of a problem is elevated AT or ALP. In longer trials, if there is no sign of liver injury after a reasonable length of exposure (e.g., 3 months), the monitoring interval can be increased to once every 2 to 3 months. Later trials also can use less frequent liver chemistry monitoring if there is no indication of hepatotoxicity.

If symptoms compatible with DILI precede knowledge of serum abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury. Reliance on early symptoms, rather than serum enzyme monitoring, has become the standard for monitoring isoniazid therapy for prophylaxis of tuberculosis and seems to prevent severe liver injury if acted upon promptly (Nolan and Goldberg et al. 1999). Attention to symptoms does not supplant routine periodic assessment of AT, TBL, and ALP in trials of investigational drugs.

3. Confirmation

In general, an increase of serum AT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious, or, of greater concern, to severe worsening if the initial abnormality was the herald of a severe reaction to follow. The need for prompt repeat testing is especially great if AT is much greater than 3xULN or TBL is greater than 2xULN. For outpatient studies, or studies in which subjects are far away from the study site, it may be difficult for the subjects to return to the study site promptly. In this case, the subjects should be retested locally, but

normal laboratory ranges should be recorded, results should be made available to study investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AT >3xULN for the subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening.

4. Close Observation

Close observation is defined as follows:

- Repeating liver tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., International Normalized Ratio (INR)).
- Considering gastroenterology or hepatology consultation.

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of a greater than 3xULN aminotransferase level is reasonable, as lesser elevations are common and nonspecific. If additional testing is done, beyond that specified in the study protocol, it is important that the subject's information be added to the case report forms or database.

5. Decision to Stop Drug Administration

It has been observed that *dechallenge* (stopping drug administration) does not always, or even usually, result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or are progressive. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity). Promptly stopping administration of the offending drug usually is the only potentially effective therapy.

A difficult question is when to stop administration of the investigational drug. Because transient rises and falls of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of study drug upon finding a greater than 3xULN

elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continuation of exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine that cause liver injury but do not cause severe DILI. On the other hand, continuing drug administration too long can be dangerous once there is marked transaminase elevation or evidence of *functional* impairment appearing after hepatocellular injury, as indicated by rising bilirubin or INR, which represent substantial damage. Although there is no published consensus on when to stop a drug in the face of laboratory abnormalities, and the decision will be affected by information on related drugs, the accumulating clinical experience, the nature of the patient, and many other factors, the following can be considered a basic guide. In general, treatment should be stopped if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

6. Evaluating Data for Alternative Causes

One of the critical purposes of close observation is to gather additional clinical information to determine the most likely cause or causes of the observed abnormalities, and specifically, whether there is a cause other than the study drug, such as one of the following common causes. Other less common causes also may need to be considered.

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute drug injury. The presence of acute viral hepatitis A, B, and C should always be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries. Also rare is liver injury caused by Epstein-Barr virus and cytomegalovirus, although this is seen more commonly in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with CMV disease.

- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, and AST >ALT, that may help distinguish it from other causes of liver injury. Autoimmune hepatitis may be acute or even fulminant in its onset; it does not always respond immediately to corticosteroids, but may have serological markers of value. Alcoholic and autoimmune hepatitis should be assessed by history and serologic testing (e.g., antinuclear antibodies).

- **Biliary tract disorders.** Biliary tract disease more often causes cholestatic injury initially and should be investigated with gall bladder and ductal ultrasound study, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension, may cause acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with spectacular increases of serum AT (e.g., AT >10,000). Cardiovascular dysfunction, including hypotension or right heart failure, should be assessed by physical examination and history.

Exclusion of the two ABCs (i.e., viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis, biliary disorders, and circulatory disorders) as causes of liver injury should be attempted in all cases of suspected DILI, and the results should be recorded. There is a practical limit as to how much testing should be done to exclude less common liver diseases, such as acute Wilson's disease or alpha-1-antitrypsin deficiency.

It is also critical to discover concomitant treatment that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures of unknown composition, nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

7. Follow-Up to Resolution

All study subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that still longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to an underlying liver disease.

8. Rechallenge

Whether or not to rechallenge a subject who showed mild DILI is a difficult question. Re-exposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with re-exposure. On the other hand, most people can adapt to xenobiotic substances such as new drugs and develop tolerance for them, as has been found even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury on isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance develops, the use of rechallenge to verify drug causation would give a false negative result.

Generally, rechallenge of subjects with significant (>5xULN) AT elevations should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge.

9. Research Opportunities

It is not known why only a few people show severe DILI in response to a hepatotoxic drug while others show nothing or seem to adapt. The current thinking is that there may be a genetic basis for such differences, but acquired factors may be equally important. The period of close observation provides a major opportunity to gather and store serial samples of blood and urine, to investigate characteristics of subjects who show evidence of mild or severe DILI, and to see how they differ from each other and from people who do not show any effects despite being similar in age, sex, and drug exposure. These serial samples can be studied by genomic, proteomic, and metabolomic methods to determine how subjects differ, and to seek biomarkers that identify the susceptible persons.

As part of the Critical Path Initiative,[3] the FDA is working with industry, academia, and other experts to broaden our understanding of the biochemical and genetic bases of DILI. In June 2006, the FDA co-sponsored a scientific workshop to determine the feasibility of developing a mathematical (in-silico) model for DILI from which other predictive experimental models can be derived to characterize potential hepatotoxicity. The long-term goal is to develop a model, or models, that can help researchers identify criteria for determining when early clinical intervention (i.e., stopping the drug) is appropriate. It is also hoped that predictive bioassays and biomarkers can be identified that will help determine which patients most likely will suffer liver toxicity from specific compounds.

This urgently needed research is not a regulatory requirement, but is an important opportunity. At present, we are able only to search among patients with drug-induced injury to predict what might happen to others. Ideally, we should seek to identify individuals at increased risk before administering a drug that they cannot tolerate. The goal is to be able to identify persons who should never be exposed to a given drug because they are idiosyncratically hypersusceptible to, or unable to recover from, DILI caused by it. If tests that screen for people susceptible to severe DILI can be developed, a hepatotoxic drug could remain available to people who are not susceptible to severe DILI, instead of having to withdraw the drug from the market, allowing no one to benefit from it.

In addition, identification of common genotypic characteristics among patients experiencing DILI in response to one or more class-related hepatotoxic agents might permit the development of in vitro or ex vivo tests or genetically altered animal strains that can be used to better predict serious hepatotoxic potential, or the lack thereof, of new drugs belonging to the same or closely related classes.

[3] See http://www.fda.gov/oc/initiatives/criticalpath.

B. Case Report Forms

In addition to collecting information on laboratory abnormalities, clinical symptoms, and the potential cause of any hepatic illness, case report forms should include the following information for cases in which liver injury is found (including control subjects with such injury):

- Time and date from start of drug administration to start of illness
- Time and date of cessation of drug, or interruption of drug administration
- Space for recording free text to describe the course of illness, including abnormalities of aminotransferases, ALP, and TBL
- Risk factors, especially alcohol use history
- Use of all concomitant drugs (dose, start and stop dates, whether drug is known to be hepatotoxic, rechallenge and dechallenge information)
- Evaluation of nondrug causes: recent hepatitis A, B, and C serology, evidence for biliary obstruction, acute alcoholic hepatitis (AST >2xALT), recent history of severe hypotension or congestive heart failure, underlying other viral disease
- Rechallenge and dechallenge information with suspect drug, with details of time and dose
- All supplemental information, including tests in local laboratories, unscheduled tests and physical exam reports, consultation reports, narrative information, and special studies

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly. Reporting should include all available information and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

C. Interpretation of Signals of DILI or Acute Liver Failure

1. Frequency and Magnitude of Liver AT Abnormalities

The presence of even a single case of severe liver failure resulting from treatment in the premarketing clinical trials database is an indicator of a high level of hepatotoxic risk. More commonly, however, there will be no identifiable cases of severe liver injury, but rather varying degrees of serum AT abnormalities that need to be interpreted. As previously noted, slight abnormalities of this kind (to <3xULN) are common in untreated and placebo-treated subjects and are not informative about the potential for the development of severe DILI.

Therefore, it has become standard practice to look at greater deviations, such as AT values ≥3x-, 5x-, or 10xULN. Because these abnormalities can occur in placebo-treated groups, it is important to compare their rate in drug-exposed subject groups relative to control groups (i.e., placebo or products that do not cause elevation of transaminases). An excess of AT abnormalities >3xULN is a signal of a potential for severe DILI, but, even though it has high sensitivity, it is not specific. Comparison of rates of AT elevations during drug treatment to a control group is probably less critical for abnormalities of greater magnitude (e.g., 10xULN), as such elevations are rarely seen spontaneously. Therefore, these greater AT elevations can be examined in the whole clinical trials database, not just in the controlled trials. It should be appreciated that serum AT activity is a relatively volatile measurement, often rising and falling

within days. It cannot be concluded from one measurement that a peak value has been seen, so that detection of an abnormal rise is a call for serial measures to determine which way the abnormality is moving, whether increasing or decreasing.

A number of factors may confound interpretation of AT abnormalities seen in NDA or BLA databases. Although the more extreme AT elevations may be better predictors of toxicity than smaller elevations, it is possible that close monitoring could affect the magnitude of abnormalities seen if it leads to earlier cessation of drug treatment that prevents the greater abnormalities from appearing. In addition, the contribution of drug treatment to an exacerbation of preexisting liver disease may be difficult to determine. Finally, normalization of abnormalities on continued treatment is not proof that the abnormality was not drug-caused, but may result from liver adaptation to the drug.

2. Combined Elevations of Aminotransferases and Bilirubin

When AT abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence of evidence for biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for severe DILI. Experience has indicated that the occurrence of even one or two well-documented cases of this combination is ominous, indicating a likelihood that the drug will cause severe liver injury.

The absence of Hy's Law cases in an NDA or BLA database may allow an estimate of an upper limit of the rate for severe DILI, using the Rule of 3 derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n study subjects if its true incidence is 1 in **n** subjects, and the group is well observed. Thus, if no cases of AT and bilirubin elevations are seen in 3,000 well-observed subjects, it can be concluded with 95 percent confidence that the true rate of such occurrences is not more than 1 per 1,000. This calculation would then suggest a rate of expected severe liver injury $\leq$1 per 10,000 exposed patients, assuming that the rate of severe injury when AT and TBL are both elevated is about 10 percent (Andrade and Lucena et al. 2005; Björnsson and Olsson 2005).

D. Analysis of Signals of DILI

Based on our experience, we recommend that the following analyses related to liver injury potential be carried out and included in an NDA or BLA, or included in an investigational new drug application when DILI is suspected and being evaluated.

1. Assessment of Drug Metabolism

The metabolism of a drug can have serious consequences for the safety profile of the drug. A drug may be metabolized to a hepatotoxic metabolite (e.g., acetaminophen, halothane, and isoniazid). Most hepatotoxic drugs have been oxidatively metabolized by the CYP450 system.

Several in vitro methods are available to detect and quantify binding for a drug or its metabolites to liver proteins, including radiochemical and immunological methods.

2. Assessment of Liver-Related Adverse Events in Controlled Trials

Analysis of incidence rates of liver-related adverse events (abnormal AT, bilirubin, and ALP levels) seen in subjects in controlled trials with at least one dose of drug exposure should be provided, generally for pooled data, although study-to-study differences may be of interest. Rates can be given as the number of events per number of subjects exposed, or as the number of events per subject-years of exposure, preferably both. For many drugs, it appears that a minimum duration of exposure is required before DILI occurs. Therefore, it is useful to give the rates of liver-related adverse events for subjects who have had the minimum duration of exposure (e.g., rate in subjects with at least 1-month exposure). Rates for pooled data should include, but are not limited to:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated bilirubin to >1.5xULN, and to >2xULN.
- Any elevations of ALP >1.5xULN.
- Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).
- Possibly liver-related deaths and liver-related treatment discontinuations. These cases should be described and time-to-event analyses should be performed. Follow-up status also should be provided. There should be a description of any histologic and rechallenge data.

All rates should be calculated separately for drug-, placebo-, and active-controlled groups. Normal ranges for all tests should be provided. Time-to-event analyses for elevated rates of significant individual events (e.g., elevated AT, bilirubin) should be provided. The contribution of sex, age, risk factors, and drug dose or regimen to the abnormalities seen should be explored.

3. Assessment of Liver-Related Adverse Events in the Entire Clinical Trials Database

Analysis of rates of liver-related adverse events (abnormal AT, bilirubin, and ALP levels) for the total clinical trials database, including subjects with exposure of at least one dose of study drug in phase 1 or phase 2 trials, or in uncontrolled, open label, extension trials should be provided. We recommend the same evaluation as for the controlled trials database discussed in section IV.D.2. Time-to-event analyses, mortality rates, study withdrawals, and similar data should be provided for significant abnormalities. The contribution of sex, age, and drug dose or regimen to the abnormalities seen should be explored.

4. Assessment of Hy's Law Cases in the Clinical Trials Database

NDA and BLA submissions should include a listing of possible Hy's Law cases identified by treatment group (e.g., subjects with any elevated AT of >3xULN, ALP <2xULN, and associated with an increase in bilirubin ≥2xULN). A narrative summary for each Hy's Law case should be provided. Narrative summaries should not only provide, in text format, the data that are already

presented in the case report tabulation, but also should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing for a better understanding of what the subject experienced. For a narrative summary to be useful, it should contain the following information:

- Subject's age, sex, weight, and height
- Discussion of signs and symptoms related to hepatotoxicity: type and timing
- Relationship of exposure duration and dose to the development of the liver injury
- Pertinent medical history
- Concomitant medications with dates and doses
- Pertinent physical exam findings
- Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)
- Time course of serum enzyme and bilirubin elevations
- A summary of all available clinical information including, if known:
  - Prior or current history of ethanol use
  - Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease
  - Symptoms and clinical course including follow-up to resolution
  - Special studies, radiologic examinations, liver biopsy results
  - Presence or absence of possible confounders, including concomitant illness, use of concomitant medications that are known hepatotoxins, such as acetaminophen
- Discussion of hepatotoxicity as supported by available clinical data and overall assessment of treating physician, consultants, and applicants as to the likelihood of DILI
- Treatment provided
- Dechallenge and rechallenge results, if done
- Outcomes and follow-up information
- Copies of hospital discharge summaries, pathology and autopsy reports

The availability of liver biopsy, explant, or autopsy slides for pathology review by review staff or external expert consultants has been helpful in the FDA's assessment of such cases. Reports of external consultant opinions solicited by the applicant should be provided to the FDA.

Complete narrative summaries that include the components previously listed also should be provided for all subjects who died of hepatic illness, or who discontinued study drugs for hepatotoxicity, including subjects with abnormalities consistent with protocol-specific stopping rules.

5. Overall Assessment of a Drug's Potential to Cause DILI

The overall assessment should characterize a drug's potential for DILI and should consider at least the following questions:

- Was liver monitoring sufficiently frequent and thorough to characterize DILI risk?
- Were there any cases of probably drug-induced serious or severe DILI?
- Were there signals of a potential for DILI (e.g., AT elevations, Hy's Law cases) and how were these signals assessed?

- What doses and durations of exposure were associated with hepatotoxicity signals?
- What approximate incidence of mild, moderate, and severe DILI could be expected postmarketing?
- Is the trial information sufficient to inform an overall risk-benefit assessment?
- Was there sufficient drug exposure (i.e., number of study subjects and duration of treatment of each study subject) and adequate liver test monitoring to reliably set an upper boundary for risk of severe DILI after marketing?
- What rate of severe injury (assuming Hy's Law cases occur at about 10 times the rate of severe injury) has been suggested or has been ruled out (e.g., no Hy's Law cases in 3,000 subjects implies a rate of such cases of <1/1,000 and thus a rate of severe DILI of <1/10,000)? This consideration should reflect the presence or absence of other signals, such as marked elevations of AT.
- Will some form of monitoring, by symptoms or serum testing, be needed? Usually, this would be considered only if there was evidence of severe liver injury or the potential for it. If so, effectiveness of monitoring in the NDA database should be discussed.

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APPENDIX A: ILLUSTRATIVE EXAMPLES OF DILI

Duract (bromfenac)

Bromfenac was a nonsteroidal anti-inflammatory drug (NSAID) studied for both short-term analgesia and long-term arthritis treatment. There was little evidence of hepatotoxicity in the short-term analgesic trials, but during longer term clinical trials in arthritis, ALT elevations >3xULN were seen in 2.8 percent of patients on bromfenac, compared to none in placebo group. Among 1,195 exposed patients, there were two cases in which there was elevated TBL as well as AT elevation in the clinical trial data submitted for review in the NDA. Concerns about possible liver toxicity led to the approval of bromfenac in July 1997 for short-term use only and not for osteoarthritis or rheumatoid arthritis. As an NSAID, however, it was prescribed long-term off-label in arthritic patients, and severe hepatotoxicity emerged. Within 6 months of approval, reports of severe hepatic failure, including two cases requiring liver transplant, were received. All severe cases involved the use of bromfenac for more than 10 days, the maximum duration of treatment recommended in the labeling.

In response, the FDA and the manufacturer strengthened the warnings in the package insert with a boxed warning, and issued a Dear Health Care Professional letter. Despite these efforts, the manufacturer and the FDA continued to receive reports of severe injuries, including reports of death or need for liver transplantation (Moses and Schroeder et al. 1999; Hunter and Johnston et al. 1999; Rabkin and Smith et al. 1999; Fontana and McCashland et al. 1999). Given the availability of other NSAIDs of equal effectiveness and safety, bromfenac was withdrawn from the market in June 1998. The two Hy's Law cases in the long-term-exposed population of about 1,000 subjects during drug development predicted an occurrence of severe hepatotoxicity during chronic use at a rate of about 1/5,000 to 10,000 people. Following approval, rates of acute liver failure for bromfenac were estimated to be in the range of 1/10,000 (Goldkind and Laine 2006).

Rezulin (troglitazone)

Troglitazone was approved by the FDA in January 1997 for the treatment of Type 2 diabetes mellitus. In reviews of the clinical trials of troglitazone conducted before approval there were no cases of liver failure among 2,510 subjects exposed to the drug in the NDA database, but 1.9 percent of troglitazone-treated subjects had ALT >3xULN compared to 0.3 percent of placebo-treated subjects, 1.7 percent had ALT >5xULN, and 0.2 percent (5 subjects) had ALT >30xULN (2 subjects in the last group also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In the Diabetes Prevention Trial at the National Institutes of Health (NIH) performed after approval, 4.3 percent of 585 troglitazone-treated subjects had ALT ≥3xULN, 1.5 percent had ALT >8xULN, and 2 subjects had ALT >30xULN, compared to 3.6 percent of subjects with ALT ≥3xULN in the placebo group (Knowler and Hamman et al. 2005). One of the subjects with ALT >30xULN developed liver failure and died, despite receiving a liver transplant. The second subject recovered. These data suggest that the rate of severe liver injury would be about 1 in 3,000 to 10,000.

After marketing, there were numerous reports (Gitlin and Julie et al. 1998; Vella and deGroen et al. 1998; Herrine and Choudary 1999) of acute liver failure associated with troglitazone use, and

four letters were sent to practicing physicians between 1997 and 1999, urging monthly monitoring and careful use. These letters did not significantly affect the monitoring done by physicians, and AT monitoring recommended in the Dear Health Care Professional letters and in the package insert was not regularly performed (Graham and Drinkard et al. 2001). Moreover, an analysis of 94 cases of liver failure reported spontaneously to the FDA showed that the progression from normal hepatic test results to irreversible liver injury occurred in less than a month (the recommended monitoring interval) in 19 patients. The onset of injury began after 3 days to more than 2 years of troglitazone use (Graham and Green et al. 2003a; Graham and Drinkard et al. 2003b). Time from jaundice to hepatic encephalopathy, liver transplantation, or death usually was rapid, averaging 24 days. Troglitazone was withdrawn from the United States market in March 2000, when other agents (rosiglitazone, pioglitazone) with similar efficacy but little or no hepatotoxicity became available.

Apart from constituting another example of the predictive value of evidence of hepatocellular injury accompanied by even two cases of elevated bilirubin, there were other lessons learned from the troglitazone experience: 1) monitoring recommendations, even after several warning letters to all practicing physicians, may not be well followed; and 2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed. In addition, following the withdrawal of troglitazone, many companies began to search for toxigenomic answers to determining individual susceptibility to DILI, and a national network was funded by NIH in 2003 to study the problem (Watkins 2005).

Exanta (ximelagatran)

Exanta (ximelagatran), an oral anticoagulant (antithrombin), was not marketed in the United States because of hepatotoxicity and other concerns discovered during clinical trials. Issues related to potential liver toxicity of ximelagatran were presented and discussed at an FDA advisory committee meeting in September 2004 (He 2004). During short-term clinical trials of the drug for prevention of thromboembolic complications after joint replacement surgical procedures, there was no increased rate of transaminase elevations in the ximelagatran group compared to the enoxaparin-warfarin group, and no serious hepatotoxicity was seen. But in longer-term (>35 days) trials in patients with chronic atrial fibrillation to prevent embolic or thrombotic strokes, an increase in ALT >3xULN occurred in 7.6 percent of 6,948 patients compared to 1.1 percent of patients receiving warfarin treatment; and 1.5 percent of ximelagatran-treated patients had ALT >10xULN.

Increases in AT typically occurred 1 to 6 months after the initiation of ximelagatran administration with peak levels within 2 to 3 months post-randomization. Among the 531 ximelagatran patients with ALT >3xULN, 39 percent completed the study on treatment, while 61 percent discontinued the drug. Almost all patients with ALT >3xULN returned to <2xULN whether the drug was stopped or not, although the return to normal was faster if ximelagatran was stopped. Of 18 patients who resumed drug after ALT returned to normal, only 2 had elevations recur. Concomitant elevations of ALT >3xULN and bilirubin >2xULN were observed in 37 of about 7,000 patients, at least 13 of whom had no alternative explanation for the concomitant ALT and bilirubin elevation. Nine of the 37 patients died, but the deaths were not

clearly hepatotoxicity-related in most cases. Only one autopsy was done and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis, but liver failure from ximelagatran might have contributed to some of the other deaths (He 2004; Lewis 2006; Kaplowitz 2006; Senior 2006; Temple 2006). Because severe hepatotoxicity was observed in an orthopedic surgery trial in an extended treatment of 35 days, Exanta was withdrawn in February 2006 from the 22 countries in which it had been approved, and further development in the United States was abandoned.

Again, short-term tolerance of ximelagatran, with resolution of even substantial elevations of ALT in most cases did not predict long-term safety. The relatively high rate of Hy's Law cases, about 0.2 percent or 1/500 (13 cases among 7,000 exposed patients), predicted the occurrence of severe hepatotoxicity, at a rate of about 1/5,000 (10 percent of the rate of Hy's Law cases). In fact, at least one death occurred among the 7,000 exposed patients subsequent liver toxicity, further supporting such an estimate.

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hepatomphalocele (hep'ă-tom-fal'ō-sēl, hep-ă-tom'fă-lō-sēl) [hepato- + omphalocele]. Hepatomphalos: umbilical hernia with involvement of the liver.

hepatomphalos (hep-ă-tom'fă-lōs). Hepatomphalocele.

hepatonecrosis (hep'ă-tō-ne-krō'sis). Death of liver cells.

hepatonephric (hep'ă-tō-nef'rik). Hepatorenal.

hepatonephromegaly (hep'ă-tō-nef'rō-meg'ă-lē) [hepato- + G. *nephros,* kidney, + *megas,* great]. Enlargement of both liver and kidney or kidneys.

hepatopathic (hep'ă-tō-path'ik). Damaging the liver.

hepatopathy (hep-ă-top'ă-thē) [hepato- + G. *pathos,* suffering]. Disease of the liver.

hepatoperitonitis (hep'ă-tō-pār'i-tō-nī'tis). Perihepatitis.

hepatopetal (hep'ă-tō-pet'al). Toward the liver, usually referring to the normal direction of portal blood flow.

hepatopexy (hep'ă-tō-pek-sē) [hepato- + G. *pēxis,* fixation]. Anchoring of the liver to the abdominal wall.

hepatophyma (hep'ă-tō-fī'mă) [hepato- + G. *phyma,* tumor]. Rounded or nodular tumor of the liver.

hepatopneumonic (hep'ă-tō-nū-mon'ik) [hepato- + G. *pneumonikos,* pulmonary]. Hepaticopulmonary; hepatopulmonary; relating to the liver and the lungs.

hepatoportal (hep'ă-tō-pōr'tăl). Relating to the portal system of the liver.

hepatoptosis (hep'ă-top-tō'sis, tō-tō'sis) [hepato- + G. *ptōsis,* a falling]. Wandering liver; a downward displacement of the liver.

hepatopulmonary (hep'ă-tō-pūl'mō-nār'ē). Hepatopneumonic.

hepatorenal (hep-ă-tō-rē'năl) [hepato- + L. *renalis,* renal, fr. *renes,* kidneys]. Hepatonephric; relating to the liver and the kidney.

hepatorrhagia (hep'ă-tō-rā'jē-ă) [hepato- + G. *rhēgnymi,* to burst forth]. Hemorrhage into or from the liver.

hepatorrhaphy (hep-ă-tōr'ă-fē) [hepato- + G. *rhaphē,* a suture]. Suture of a wound of the liver.

hepatorrhea (hep'ă-tō-rē'ă) [hepato- + G. *rhoia,* a flow]. Obsolete term for cholorrhea.

hepatorrhexis (hep'ă-tō-rek'sis) [hepato- + G. *rhēxis,* rupture]. Rupture of the liver.

hepatoscopy (hep-ă-tos'kŏ-pē) [hepato- + G. *skopeō,* to examine]. Examination of the liver.

hepatosplenitis (hep'ă-tō-splē-nī'tis). Inflammation of the liver and spleen.

hepatosplenography (hep'ă-tō-splē-nog'ră-fē). Hepatolienography; the use of a contrast medium to outline or depict the liver and spleen roentgenographically.

hepatosplenomegaly (hep'ă-tō-splē-nō-meg'ă-lē) [hepato- + G. *splēn,* spleen, + *megas,* large]. Hepatolienomegaly; enlargement of the liver and spleen.

hepatosplenopathy (hep'ă-tō-splē-nop'ă-thē). Disease of the liver and spleen.

hepatostomy (hep-ă-tos'tō-mē) [hepato- + G. *stoma,* mouth]. Establishment of a fissure into the liver.

hepatotherapy (hep'ă-tō-thār'ă-pē). 1. Treatment of disease of the liver. 2. Therapeutic use of liver extract or of the raw substance of the liver.

hepatotomy (hep-ă-tot'ō-mē) [hepato- + G. *tomē,* incision]. Incision into the liver.

hepatotoxemia (hep'ă-tō-tok-sē'mē-ă) [hepato- + G. *toxikon,* poison, + *haima,* blood]. Autointoxication assumed to be due to improper functioning of the liver.

hepatotoxic (hep'ă-tō-tok'sik). Relating to an agent that damages the liver, or pertaining to any such action.

hepatotoxin (hep'ă-tō-tok'sin). A toxin that is destructive to parenchymal cells of the liver.

Hepatozoon (hep'ă-tō-zō'on) [hepato- + G. *zōon,* animal]. A genus of coccidian parasites (family Haemogregarinidae), in which schizogony occurs in the visceral organs, gametogony in the leukocytes or erythrocytes of vertebrate animals, and sporogony in certain ticks and other blood-sucking invertebrates. *H. canis* occurs in dogs, cats, jackals, and hyenas, but is most pathogenic in dogs, in which it may cause serious disease and death; other species have been described from rats, mice, rabbits, and squirrels.

hepta- [G. *hepta,* seven]. Prefix denoting seven.

heptabarbital (hep-tă-bar'bi-tawl). 5-(1-Cyclohepten-1-yl)-5-ethyl-barbituric acid; a short-acting barbiturate that produces sedation, hypnosis, or anesthesia, depending upon the dose administered.

heptad (hep'tad). A septivalent chemical element or radical.

heptaminol (hep-tam'i-nol). 6-Amino-2-methyl-2-heptanol; a sympathomimetic, vasoconstrictor, and cardiotonic.

heptanal (hep'tă-năl). Enanthal; heptaldehyde; $CH_3(CH_2)_5CHO$; obtained from the ricinoleic acid of castor oil by chemical means; used in the manufacture of ethyl oenanthate, a constituent of many artificial essences (flavors).

heptazone hydrochloride (hep'tă-zōn). Phenadoxone hydrochloride.

heptose (hep'tōs). A sugar with 7 carbon atoms in its molecule; e.g., sedoheptulose.

heptulose (hep'tū-lōs). Ketoheptose.

D-*altro*-2-heptulose. Sedoheptulose.

D-*manno*-heptulose. A ketoheptose of the mannose configuration, occurring in the urine of individuals who have eaten a large quantity of avocados.

Herbert, Herbert, British ophthalmic surgeon, 1865–1942. See H.'s *operation.*

herbivorous (her-biv'ŏ-rŭs) [L. *herba,* herb, + *voro,* to devour] Feeding on plants.

Herbst, Ernst F.G., German anatomist, 1803–1893. See H.'s *corpuscles.*

herd. 1. A group of people or animals in a given area. 2. An immunologic concept of an ecologic composite that includes susceptible animal species (including man), vectors, and environmental factors.

hereditary (hĕ-red'i-ter-ē) [L. *hereditarius:* fr. *heres* (*hered-*), an heir]. Transmitted from parent to offspring; derived from ancestry; obtained by inheritance.

heredity (hĕ-red'i-tē) [L. *hereditas,* inheritance, fr. *heres* (*hered-*), heir]. The transmission of characters from parent to offspring.

heredo- [L. *heres,* an heir]. Prefix denoting heredity.

heredoataxia (her'ĕ-dō-ă-tak'sē-ă). Hereditary spinal *ataxia.*

heredofamilial (her'ĕ-dō-fă-mil'ē-ăl). Obsolete term denoting an inherited condition present in more than one member of a family.

heredopathia atactica polyneuritiformis (her'ĕ-dō-path'ē-ă ă-tak'ti-kă pol'ē-nū-rī-ti-fōr'mis). Refsum's *disease.*

Herelle, Felix H. See d'Herelle, Felix H.

Herellea (hĕ-rel'ē-ă). A bacterial generic name which has been officially rejected because its type species, *H. vaginicola,* is a member of the genus *Acinetobacter.*

Hering, Heinrich Ewald, German physiologist, 1866–1948. See sinus *nerve* of H; H.-Breuer *reflex;* Traube-H. *curve.*

Hering, Karl E.K., German physiologist, 1834–1918. See H.'s *test, theory: canal* of H.; Traube-H. *curves, waves;* Semon-H. *theory.*

heritability (her'i-tă-bil'i-tē) [see heredity]. 1. In intelligence or per-

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able 69-1—*(continued)*

linical Manifestations of Adverse Reactions to Drugs

VII. RESPIRATORY MANIFESTATIONS

Airway obstruction (bronchospasm, asthma; see also anaphylaxis)
- Adenosine
- Beta blockers
- Cephalosporins
- Cholinergic drugs
- NSAIDs, e.g., aspirin, indomethacin
- Penicillins
- Pentazocine
- Streptomycin
- Tartrazine (drugs with yellow dye)

Cough
- ACE inhibitors

Nasal congestion
- Decongestant abuse
- Guanethidine
- Isoproterenol
- Oral contraceptives
- Reserpine

Pulmonary edema
- Contrast media
- Heroin
- Hydrochlorthiazide
- Interleukin 2
- Methadone
- Propoxyphene

Pulmonary hypertension
- Fenfluramine

Pulmonary infiltrates
- Acyclovir
- Amiodarone
- Azothioprine
- Bleomycin
- Busulfan
- Carmustine (BCNU)
- Chlorambucil
- Cyclophosphamide
- Gold
- Melphalan
- Methotrexate

Pulmonary infiltrates (*cont.*)
- Methysergide
- Mitomycin C
- Nitrofurantoin
- Procarbazine
- Sulfonamides

Respiratory depression
- Aminoglycosides
- Hypnotics
- Opiates
- Polymyxins
- Sedatives
- Trimethaphan

VIII. GASTROINTESTINAL MANIFESTATIONS

Cholestatic hepatitis
- Acetohexamide
- Anabolic steroids
- Androgens
- Chlorpropamide
- Clavulanic acid/amoxicillin
- Cyclosporine
- Erythromycin estolate
- Flucloxacillin
- Gold salts
- Methimazole
- Nitrofurantoin
- Oral contraceptives
- Phenothiazines

Constipation or ileus
- Aluminum hydroxide
- Barium sulfate
- Calcium carbonate
- Ferrous sulfate
- Ganglionic blockers
- Ion exchange resins
- Opiates
- Phenothiazines
- Tricyclic antidepressants
- Verapamil

Diarrhea or colitis
- Antibiotics (broad-spectrum)
- Clindamycin
- Cocaine
- Colchicine
- Digitalis
- Guanethidine
- Lactose excipients
- Lincomycin
- Magnesium in antacids
- Methyldopa
- Misoprostol
- Oral contraceptives
- Purgatives
- Reserpine
- Ticlopidine

Diffuse hepatocellular damage
- Acetaminophen (paracetamol)
- Acebutolol
- Allopurinol
- Aminosalicylic acid
- Amiodarone
- Aprindine
- Carbenicillin
- Cyclophosphamide
- Dapsone
- Diclofenac
- Erythromycin estolate
- Ethionamide
- Felbamate
- Glyburide
- Halothane
- Isoniazid
- Ketoconazole
- Labetalol
- Lovastatin
- Methimazole
- Methotrexate
- Methoxyflurane
- Methyldopa
- Monoamine oxidase inhibitors
- Niacin
- Nifedipine
- Nitrofurantoin
- Oxyphenisatin
- Phenytoin and other hydantoins
- Propoxyphene
- Propylthiouracil
- Pyridium
- Quinidine
- Rifampin
- Salicylates
- Sodium valproate
- Sulfonamides
- Tacrine
- Tetracyclines
- Trazodone
- Verapamil
- Zidovudine (AZT)

Gallstones/biliary pseudolithiasis
- Ceftriaxone

Intestinal ulceration
- Solid KCl preparations

Malabsorption
- Aminosalicylic acid
- Antibiotics (broad-spectrum)
- Cholestyramine
- Colchicine
- Colestipol
- Cytotoxic agents
- Neomycin
- Phenobarbital
- Phenytoin
- Primidone

Nausea or vomiting
- Digitalis
- Estrogens
- Ferrous sulfate
- Levodopa
- Opiates
- Potassium chloride
- Tetracyclines
- Theophylline

Oral conditions
- Dental discoloration:
  - Tetracycline
- Dry mouth:
  - Anticholinergics
  - Clonidine
  - Levodopa
  - Methyldopa
  - Tricyclic antidepressants
- Gingival hyperplasia:
  - Calcium antagonists
  - Cyclosporine
  - Phenytoin
- Salivary gland swelling:
  - Bethanidine
  - Bretylium
  - Clonidine

Oral conditions
- Salivary gland swelling (*cont.*)
  - Guanethidine
  - Iodides
  - Phenylbutazone
- Taste disturbances:
  - Acetazolamide
  - Biguanides
  - Captopril
  - Griseofulvin
  - Lithium
  - Metronidazole
  - Penicillamine
  - Rifampin
- Ulceration:
  - Aspirin
  - Cytotoxic agents
  - Gentian violet
  - Isoproterenol (sublingual)
- Pancreatin

Pancreatitis
- Asparaginase
- Azathioprine
- Didanosine
- Estrogens
- Ethacrynic acid
- Furosemide
- Glucocorticoids
- Mercaptopurine
- Opiates
- Oral contraceptives
- Pentamidine
- Sulfonamides
- Thiazides
- Valproic acid

Peptic ulceration or hemorrhage
- Aspirin
- Ethacrynic acid
- Glucocorticoids
- NSAIDs†
- Reserpine (large doses)

(continued)

Table 296-2

Principal Alterations of Hepatic Morphology Produced by Some Commonly Used Drugs and Chemicals*

Principal Morphologic Change	Class of Agent	Example
Cholestasis	Anabolic steroid	Methyl testosterone.
	Anti-inflammatory	Sulindac
	Antithyroid	Methimazole
	Antibiotic	Erythromycin estolate, nitrofurantoin, rifampin
	Oral contraceptive	Norethynodrel with mestranol
	Oral hypoglycemic	Chlorpropamide
	Tranquilizer	Chlorpromazine†
	Oncotherapeutic	Anabolic steroids, busulfan, tamoxifen
	Immunosuppressive	Cyclosporine
	Anticonvulsant	Carbamazine
	Calcium channel blocker	Nifedipine, verapamil
Fatty liver	Antibiotic	Tetracycline
	Anticonvulsant	Sodium valproate
	Antiarrhythmic	Amiodarone
	Antiviral	Dideoxynucleosides (e.g., zidovudine)
	Oncotherapeutic	Asparaginase, methotrexate
Hepatitis	Anesthetic	Halothane‡
	Anticonvulsant	Phenytoin, carbamazine
	Antihypertensive	Methyldopa,‡ captopril, enalapril
	Antibiotic	Isoniazid,‡ rifampin, nitrofurantoin
	Diuretic	Chlorothiazide
	Laxative	Oxyphenisatin‡
	Antidepressant	Iproniazid, amitriptyline, imipramine
	Anti-inflammatory	Ibuprofen, indomethacin, diclofenac, sulindac
	Antifungal	Ketoconazole, fluconazole, itraconazole
	Antiviral	Zidovudine, dideoxy inosine
	Calcium channel blocker	Nifedipine, verapamil, diltiazem
	Antiandrogen	Flutamide
Mixed hepatitis/ cholestatic	Immunosuppressive	Azathioprine
	Lipid-lowering	Nicotinic acid, lovastatin
Toxic (necrosis)	Hydrocarbon	Carbon tetrachloride
	Metal	Yellow phosphorus
	Mushroom	*Amanita phalloides*
	Analgesic	Acetaminophen
	Solvent	Dimethylformamide
Granulomas	Anti-inflammatory	Phenylbutazone
	Antibiotic	Sulfanomides
	Xanthine oxidase inhibitor	Allopurinol
	Antiarrhythmic	Quinidine
	Anticonvulsant	Carbamazine

* Several agents cause more than one type of liver lesion and appear under more than one category.
† Rarely associated with primary biliary cirrhosis–like lesion.
‡ Occasionally associated with chronic hepatitis or bridging hepatic necrosis or cirrhosis.

angiosarcoma of the liver. Oral contraceptives have been implicated in the development of hepatic adenoma and, rarely, hepatocellular carcinoma and occlusion of the hepatic vein (Budd-Chiari syndrome). Another unusual lesion, peliosis hepatis (blood cysts of the liver), has been observed in some patients treated with anabolic steroids. The existence of these hepatic disorders expands the spectrum of liver injury induced by chemical agents and emphasizes the need for a thorough drug history in all patients with liver dysfunction.

The following are the patterns of adverse hepatic reactions for some prototypic agents.

ACETAMINOPHEN HEPATOTOXICITY (DIRECT TOXIN) Acetaminophen has caused severe centrolobular hepatic necrosis when ingested in large amounts in suicide attempts or accidentally by children. A single dose of 10 to 15 g, occasionally less, may produce clinical evidence of liver injury. Fatal fulminant disease is usually (although not invariably) associated with ingestion of 25 g or more. Blood levels of acetaminophen correlate with the severity of hepatic injury (levels above 300 μg/mL 4 h after ingestion are predictive of the development of severe damage, while levels below 150 μg/mL suggest that hepatic injury is highly unlikely). Nausea, vomiting, diarrhea, abdominal pain, and shock are early manifestations occurring 4 to 12 h after ingestion. Then 24 to 48 h later, when these features are abating, hepatic injury becomes apparent. Maximal abnormalities and hepatic failure may not be evident until 4 to 6 days after ingestion, and aminotransferase levels approaching 10,000 units are not uncommon. Renal failure and myocardial injury may be present.

Acetaminophen hepatotoxicity is mediated by a toxic reactive metabolite formed from the parent compound by the cytochrome P450 mixed-function oxidase system of the hepatocyte. This metabolite is detoxified by binding to glutathione. When excessive amounts of the metabolite are formed, glutathione levels in the liver fall, and the metabolite is covalently bound to nucleophilic hepatocyte macromolecules. This process is believed to lead to hepatocyte necrosis; the precise sequence and mechanism are unknown. Hepatic injury may be potentiated by prior administration of alcohol or other drugs, by conditions that stimulate the mixed-function oxidase system, or by conditions such as starvation that reduce hepatic glutathione levels. Cimetidine, which inhibits P450 enzymes, has the potential to reduce generation of the toxic metabolite. In chronic alcoholics, the toxic dose of acetaminophen may be as low as 2 g.

Rx TREATMENT

Treatment of acetaminophen overdosage includes gastric lavage, supportive measures, and oral administration of activated charcoal or cholestyramine to prevent absorption of residual drug. Neither of these agents appears to be effective if given more than 30 min after acetaminophen ingestion; if they are used, the stomach lavage should be done before other agents are administered orally. In patients with high acetaminophen blood levels (>200 μg/mL measured at 4 h or >100 μg/mL at 8 h after ingestion), the administration of sulfhydryl compounds (e.g., cysteamine, cysteine, or *N*-acetylcysteine) appears to reduce the severity of hepatic necrosis. These agents appear to act by providing a reservoir of sulfhydryl groups to bind the toxic metabolites or by stimulating synthesis and repletion of hepatic glutathione. Therapy should be begun within 8 h of ingestion but may be effective even if given as late as 24 to 36 h after overdose. Later administration of sulfhydryl compounds is of uncertain value. Routine use of *N*-acetylcysteine has reduced substantially the occurrence of fatal acetaminophen hepatotoxicity. When given orally, *N*-acetylcysteine is diluted to yield a 5% solution. A loading dose of 140 mg/kg is given, followed by 70 mg/kg every 4 h for 15 to 20 doses. Treatment can be stopped when plasma acetominophen levels indicate that the risk of liver damage is low.

Survivors of acute acetaminophen overdose usually have no evidence of hepatic sequelae. In a few patients, prolonged or repeated administration of acetaminophen in therapeutic doses appears to have led to the development of chronic hepatitis and cirrhosis.

HALOTHANE HEPATOTOXICITY (IDIOSYNCRATIC REACTION) Administration of halothane, a nonexplosive fluorinated hydrocarbon anesthetic agent that is structurally similar to chloroform, results in severe hepatic necrosis in a small number of individuals, many of whom have previously been exposed to this agent. The failure to produce similar hepatic lesions reliably in animals, the rarity of hepatic impairment in human beings, and the delayed appearance

FDA panel wants stronger acetaminophen warnings

A US advisory panel has recommended that explicit warnings about the possibility of liver toxicity should be added to all packs of OTC products containing acetaminophen (paracetamol). Although the risk of hepatotoxicity with the product is low statistically, in numerical terms it is high, with several hundred people dying each year. McNeil Consumer & Specialty Products, which presented data showing that the drug is safe at the recommended dosages, has already decided to add such a warning to its top-selling Tylenol line.

The US FDA's non-prescription drugs advisory committee met on September 19th for the first day of a two-day session to review the safety of several OTC analgesics, beginning with acetaminophen. Panellists said all OTC products in which acetaminophen is an active ingredient, such as cough-cold medicines, should clearly state this on the front of the pack.

However, except in the case of high alcohol use, it decided that there was insufficient information to require warnings about a higher risk of liver damage due to other possible risk factors, such as underlying liver disease, use of other drugs or malnourishment.

Acetaminophen labelling currently instructs users who consume three or more alcoholic drinks a day to ask their doctor whether they should take acetaminophen or other pain relievers/fever reducers. However, the committee said the specific warning about hepatotoxicity associated with acetaminophen should be kept separate from this instruction, so that users would not conclude that only alcohol consumption can lead to liver damage.

. . . hepatotoxicity risk

Annual overdoses associated with acetaminophen result in 56,000 emergency department visits each year, including 26,000 hospitalisations and more than 400 deaths, reported Dr William Lee, professor of liver disease at the University of Texas Southwestern Medical Center in Dallas. However, Dr Debra Bowen, McNeil's vice-president for R&D, noted that more than 100 million Americans consume acetaminophen preparations each year. "Harm is rare," she said.

Dr Lee said about two-thirds of the overdoses were suicide attempts. Nevertheless, more than 2,000 hospitalisations and 100 deaths a year can be attributed to unintentional acetaminophen-associated overdoses, he said. The FDA asked the advisory committee to focus on these cases, on the assumption that label and pack changes could not reduce the number of suicide attempts.

That assumption was challenged by Dr Peter Lurie of the US consumer advocacy organisation, Public Citizen. "In fact, many countries have sought to address the problem of suicides or 'intentional overdoses'," he said. In the UK, for example, an experiment implemented in September 1998 restricted the number of acetaminophen tablets per pack to 16 in supermarkets and 32 in pharmacies, primarily through the use of blister packs. "Although one can buy several packs, prescriptions are required to obtain more than 100 tablets."

Early evaluation of the programme has shown decreases in total and severe acetaminophen overdoses as well as decreases in acetaminophen-overdose liver transplants and deaths, although the results are not completely consistent between studies, Dr Lurie said.

A member of the audience rose to inform the committee that acetaminophen sales in the UK had dropped by half since the restrictions came into effect. Aspirin sales also declined, but the use of other analgesics, including ibuprofen, had doubled, he said. But Dr Charles Ganley, director of the FDA's division of OTC drug products, said the agency would have to have good justification to restrict pack sizes in the same way. Such a move would need clearances from numerous bodies, such as the White House Office of Management and Budget. "And if we don't have data to support that, it's very difficult to impose it on someone," Dr Ganley said.

. . . lack of information

Unintended overdosing is usually caused by lack of information, the committee was told. The mother of a young man who died of liver failure after taking acetaminophen plus codeine and then OTC acetaminophen said that everyone had thought it was safe.

"We continue to meet doctors who are unaware of the frequency of acetaminophen toxicity," she said. "Most people know about stomach problems and bleeding associated with NSAIs. Why aren't they aware of acetaminophen liver problems?"

Dr Susan Winckler, vice-president and staff counsel of the American Pharmaceutical Association, said a study by the National Council on Patient Information and Education (NCPIE) on OTC medications had found that only 34% of consumers read label information about the active ingredient, and only 21% read the warnings section.

Only 28% of parents and other "caregivers" were aware that OTCs could have side-effects, and only 36% could name a possible side-effect for a given medication. Most panelists wanted the FDA, which does not regulate OTC advertising, to recommend to the Federal Trade Commission, which does, that it require acetaminophen manufacturers to warn of liver toxicity in their TV and print ads.

In the US, the recommended dose of acetaminophen for adults is 4g per day. McNeil consultant Dr Richard Dart, director of the Rocky Mountain Poison & Drug Center in Colorado, said prospective studies indicate no toxicity at or near the recommended dose. The studies also showed that serious hepatotoxicity occurs following substantial overdose, either a single dose of about 15g or multiple doses of around 12g/day.

However, Dr Claudia Karwoski of the FDA's Office of Drug Safety found 23 cases of severe liver injury with acetaminophen at doses of 4g or less per day in the FDA's Adverse Event Reporting System (AERS) database. Ten of these cases were associated with alcoholism or alcohol use, three with regular alcohol use, 13 with liver problems, and three with poor nutrition status.

Dr Karwoski said it was difficult to draw conclusions from these cases, as there was no certainty that the dosing information was reliable or that the cases were unintentional. On the other hand, the FDA estimates that only 1-10% of adverse events are reported to it, she said.

from which the company reported results in November (*Scrip* No 3316, p 19). It met its primary endpoint, median time to onset of relief of symptoms, with a 20 units/kg dose – 30 minutes versus 1.5 hours with placebo. A 10 units/kg dose showed a trend towards improvement which did not reach significance, but CSL declined to give the precise data.

The trial also met all its secondary endpoints, including worsening of symptoms and time to complete resolution of HAE symptoms.

There are no specifically approved therapies in the US for HAE, a genetic disorder thought to affect up to 75,000 people in the US and Europe that causes recurrent attacks of inflammation in the extremities, face, urogenital tract, abdomen and larynx. Laryngeal attacks can be fatal.

It is caused by a deficiency of the plasma protein C1 esterase inhibitor, which in healthy people decreases activity of the complement and kallikrein systems which are responsible for the inflammation seen in the disorder.

Current treatments include anabolic steroids to prevent attacks, and pain control and rehydration, or antifibrinolytics such as tranexamic acid during attacks; however, patients often have to wait for the pain and swelling to subside. CSL has marketed C1-INH as Berinert in several European countries for 30 years including Germany, Austria and Switzerland. CSL said it had developed the product in the US after becoming aware of the growing unmet need there in recent years. The firm does have plans to file it in the EU, but declined to say when.

...competition

There are several products vying to become the first specifically approved treatment for HAE in the US. Lev Pharmaceuticals filed its candidate Cinryze in the US in August, while Jerini filed icatibant (proposed tradename Firazyr) in the US in October and in the EU last August. Pharming had a setback when its product Rhucin was rejected by the EU's CHMP in December (*Scrip* No 3322, p 21), but the firm has appealed the decision and plans to file Rhucin in the US later this year.

C1-INH, Cinryze and Rhucin are all C1-inhibitors, with the first two being derived from human plasma, while Rhucin is a transgenic product derived from rabbits' milk. Lev says its product goes through a further filtration process to eliminate contaminants, while Pharming says that Rhucin does not carry the same risk of contamination as plasma-derived products and is not limited by the availability of human blood.

Icatibant is a bradykinin B2 antagonist, working later in the inflammatory cascade – bradykinin is produced via kallikrein activation. Another candidate, Dyax's DX-88 (ecallantide), a plasma kallikrein inhibitor, is in a confirmatory Phase III trial.

C1-INH appears to compare well with the other candidates, which also had the primary endpoint of time to onset of symptom relief in clinical trials. This was 60 minutes with Rhucin versus 8.5 hours with placebo (*Scrip* No 3291, p 19), two hours for Cinryze versus over four hours with placebo (*Scrip* No 3283, p 21), and two hours with icatibant compared with 12 hours for tranexamic acid.

can result in fatalities when overdosed. Other approved cough products containing the narcotic ingredient are given every four to six hours, and the regulators continue to review safety information for those products.

Adverse event reports associated with Tussionex have included life-threatening side-effects and deaths in patients, including children, the regulators said. These reports reveal that physicians are sometimes prescribing, and patients are sometimes taking, more than the recommended dose or taking the medication more frequently than every 12 hours. The reports also show that Tussionex is sometimes prescribed or given to children less than six years old, for whom the medication is not approved.

Without careful measurement of the suspension, overdose can result in fatal respiratory depression. UCB has agreed to update the labelling to make it clear that Tussionex is contraindicated in children under six, and that accurate dosing is essential. The FDA urged that physicians and caregivers only use a medical syringe or other device designed to measure the suspension – and that household teaspoons or tablespoons vary in size and should not be used.

The company has said that five deaths have been reported in children under age six who took Tussionex since its approval in the US in 1987. Tussionex contains hydrocodone and the antihistamine chlorpheniramine in an extended-release form.

US liver warning for Prezista

Tibotec Therapeutics (Johnson & Johnson), in co-operation with the FDA, has alerted US doctors of changes to the "Warnings" section of the data sheet for its protease inhibitor, Prezista (darunavir), regarding the risk of hepatotoxicity. Prezista was introduced in the US in 2006 for the treatment of HIV/AIDS.

The alert was made in a Dear Healthcare Provider letter that has been posted on the FDA's Medwatch page. The letter notes that in clinical trials and postmarketing experience, drug-induced hepatitis (eg, acute hepatitis, cytolytic hepatitis) has been reported in patients receiving combination therapy with Prezista/ritonavir. Ritonavir is marketed by Abbott as Norvir.

The letter notes that the updated data sheet states under the heading "hepatotoxicity" that during clinical trials in 3,063 patients, drug-induced hepatitis was reported in 0.5% of patients receiving the combination. Patients with pre-existing liver dysfunction have an increased risk for liver function abnormalities.

That section of the data sheet now also notes: "Postmarketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with Prezista/ritonavir therapy has not been established." The number of postmarketing cases has not been provided in the updated label. Tibotec's letter states that appropriate laboratory tests should be conducted prior to initiating therapy with Prezista.

Swedish generics firms complain about substitution

The Swedish generic industry association, the FGL, has written to the Medical Products Agency complaining about the generic substitution list, which it says is becoming too restricted. A number of generic products have been excluded from the list because the MPA says they are not identical to the original, the FGL says.

Generic substitution was introduced in Sweden in October 2002. The MPA draws up a list of substitutable products, and pharmacists dispense the cheapest product they have in stock.

But the FGL says the system needs to be reviewed to ensure that the substitution criteria correspond with the intention of the law. It also wants the MPA to improve its communications with generics companies during the procedure for deciding on substitution status, in order to avoid obstacles to substitution.

It says the MPA has developed its own regulation separately from the original law, so that it is in charge of both the regulation and its implementation. The FGL points out that when generics companies applied for approval they assumed the products would also be added to the substitution list. Therefore it is important for the MPA to communicate if there are any problems, as this could affect the company's market prospects.

...examples

The FGL refers to two examples from a previous letter to the MPA: Nycomed's anti-epileptic, Gabapentin Nycomed (gabapentin), was not considered substitutable for Pfizer's Neurontin (gabapentin) for epilepsy. The agency said the product had a narrow therapeutic window and so it could not rule out the possibility that switching a patient from the original product to a generic could cause problems. The possibility that the prescriber might identify such risks in advance was limited.

Another was GEA's Fluconazol GEA (fluconazole), which was approved under the European mutual recognition procedure. The MPA decided not to list the product, saying differences in its labelling meant it was not substitutable for the originator, Pfizer's Diflucan. The general manager of GEA in Sweden, Hakan Josephsson, told *Scrip* that the labelling had now been changed and the product would be added to the substitution list. But if the MPA had told the company about this problem earlier on, it could have been resolved more quickly, he said.

The FGL says that in both cases it would have been better if the MPA had contacted the companies to inform them about the reasons for its decisions and to find a solution. The consequence of a restrictive substitution approach is less competition and therefore fewer saving opportunities for taxpayers, according to the association. "For the companies that market generics it means insecurity and the risk that investments will not yield economic returns," it says.

...agency reply

The agency said it would reply in writing or invite the FGL for a meeting to discuss the issue. It said the substitution regulation and the agency's overall criteria for the list had been published in 2002; the law said that only products that were medically equivalent should be added to the list. The agency had then developed its criteria for the listing

EMEA looks at early detection of hepatotoxicity

The European Medicines Agency (EMEA) is preparing guidance for the pharmaceutical industry on ways of detecting a product's hepatotoxicity potential before it enters clinical trials.

Liver injury is one of the most common reasons why approved drugs are withdrawn from the market, and over the past few years several products have been withdrawn or discussed by the agency's scientific advisory committee, the CHMP, for this reason, the EMEA says. The CHMP's pharmacovigilance working party has discussed more than 20 products because of signs of liver damage.

None of the current guidelines looks at how to detect and collect early signals linked to drug-induced liver injury in non-clinical studies, and experience shows that using traditional reporting strategies may be insufficient to predict the outcome of serious adverse liver effects in humans, the agency notes.

It has therefore issued a concept paper as a first step towards developing a CHMP guideline on early detection of hepatotoxicity from non-clinical documentation. This will help industry and regulatory assessors to evaluate and interpret non-clinical data that could possibly serve as prognostic early signals. The draft guideline is expected to be discussed at the December meeting of the CHMP's safety working party.

■ Medicine spending up by 6.5% in Norway

Medicine spending in Norway grew by 6.5% to NKr4.8 billion ($700 million) during the first six months of this year compared with the same period last year, according to Farmastat. The generics sector saw the strongest growth rate, with sales up by 8.8% to NKr596 million. Sales of parallel imports fell by 6% to NKr283 million. Sales of non-prescription products through pharmacies also declined, by 0.9% to NKr365 million, partly as a result of the liberalisation of the OTC market in Norway last year. Sales of medicines had slowed down in 2003, when the growth rate was only 3.3% compared with double digit growth rates in previous years (*Scrip* No 2948, p 8).

■ UK sales of athlete's foot products could grow by 16% this year

The switching of products to general sales list (GSL) status in the UK can have beneficial effects on pharmacy sales, according to Novartis Consumer Health. The switch of its Lamisil (terbinafine) 1% spray to GSL from August 1st, combined with the switch of Lamisil 1% cream to GSL in March, is expected to contribute to an estimated 16% growth in the market for athlete's foot products this year, the company says. 70% of such sales are of GSL products, and 66% of GSL sales are in pharmacies, so pharmacies should benefit from the switch. The total UK market for athlete's foot products is estimated at £20.3 million.

■ EU pays more into Global Fund

The European Commission is to pay an additional €42 million to the Global Fund to fight HIV/AIDS, TB and Malaria, bringing its total contribution since 2002 to €375 million,

—Cont.

rved During the Premarketing Evaluation of his section reports event frequencies evaluated · 1988 for adverse events occurring in a group of ·ly 1800 patients who took multiple doses of 'he conditions and duration of exposure to ·ied greatly, involving well-controlled studies as ·rience in open and uncontrolled clinical set- absence of appropriate controls in some of the ausal relationship between these events and ith pergolide cannot be determined.
ng enumeration by organ system describes rms of their relative frequency of reporting in -e. Events of major clinical importance are also the Warnings and Precautions sections.
g definitions of frequency are used: frequent ad- are defined as those occurring in at least 1/100 requent adverse events are those occurring in)00 patients; rare events are those occurring in 1/1000 patients.

/hole — *Frequent:* headache, asthenia, accidenain, abdominal pain, chest pain, back pain, flu eck pain, fever; *Infrequent:* facial edema, chills, domen, malaise, neoplasm, hernia, pelvic pain, litis, moniliasis, abscess, jaw pain, hypothercute abdominal syndrome, LE syndrome.

ılar System — *Frequent:* postural hypotension, pertension, palpitations, vasodilatations, conrt failure; *Infrequent:* myocardial infarction, heart arrest, abnormal electrocardiogram, anis, thrombophlebitis, bradycardia, ventricular s, cerebrovascular accident, ventricular tachybral ischemia, atrial fibrillation, varicose vein, embolus, AV block, shock; *Rare:* vasculitis, pulertension, pericarditis, migraine, heart block, norrhage.

/stem — *Frequent:* nausea, vomiting, dyspepsia, nstipation, dry mouth, dysphagia; *Infrequent:* bnormal liver function tests, increased appetite, nd enlargement, thirst, gastroenteritis, gastriıtal abscess, intestinal obstruction, nausea and ngivitis, esophagitis, cholelithiasis, tooth caries, omach ulcer, melena, hepatomegaly, hematemtion; *Rare:* sialadenitis, peptic ulcer, pancreati-, glossitis, fecal incontinence, duodenitis, colitis, , aphthous stomatitis, esophageal ulcer.

ystem — *Infrequent:* hypothyroidism, adenoma, ·litus, ADH inappropriate; *Rare:* endocrine disid adenoma.

Lymphatic System — *Frequent:* anemia; *Infre*openia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; ıra, lymphocytosis, eosinophilia, thrombocythe- lymphoblastic leukemia, polycythemia, splenomegaly.

ınd Nutritional System — *Frequent:* peripheral ght loss, weight gain; *Infrequent:* dehydration, a, hypoglycemia, iron deficiency anemia, hyperout, hypercholesteremia; *Rare:* electrolyte imbalxia, acidosis, hyperuricemia.

eletal System — *Frequent:* twitching, myalgia, *Infrequent:* bone pain, tenosynovitis, myositis, na, arthritis; *Rare:* osteoporosis, muscle atrophy, is.

/stem — *Frequent:* dyskinesia, dizziness, hallucinfusion, somnolence, insomnia, dystonia, paresression, anxiety, tremor, akinesia, extrapyramiome, abnormal gait, abnormal dreams, ion, psychosis, personality disorder, nervousoathetosis, amnesia, paranoid reaction, abnorıg; *Infrequent:* akathisia, neuropathy, neuralgia, delusions, convulsion, libido increased, euphonal lability, libido decreased, vertigo, myoclonus, hy, paralysis, neurosis, hyperkinesia, ataxia, ı syndrome, torticollis, meningitis, manic reacinesia, hostility, agitation, hypotonia; *Rare:* stuis, intracranial hypertension, hemiplegia, facial rain edema, myelitis, hallucinations and confuıbrupt discontinuation.

/ System — *Frequent:* rhinitis, dyspnea, pneuıryngitis, cough increased; *Infrequent:* epistaxis, usitis, bronchitis, voice alteration, hemoptysis, ng edema, pleural effusion, laryngitis, emphyea, hyperventilation; *Rare:* pneumothorax, lung rynx edema, hypoxia, hypoventilation, hemothoma of lung.

ppendages System — *Frequent:* sweating, rash; skin discoloration, pruritus, acne, skin ulcer, alskin, skin carcinoma, seborrhea, hirsutism, herx, eczema, fungal dermatitis, herpes zoster; *Rare:* llous rash, subcutaneous nodule, skin nodule, n neoplasm, lichenoid dermatitis.

nses System — *Frequent:* abnormal vision, dip- *quent:* otitis media, conjunctivitis, tinnitus, deaf- perversion, ear pain, eye pain, glaucoma, eye e, photophobia, visual field defect; *Rare:* blind- retinal detachment, retinal vascular hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

Postintroduction Reports — Voluntary reports of adverse events temporally associated with pergolide that have been received since market introduction and which may have no causal relationship with the drug, include the following: neuroleptic malignant syndrome and Raynaud's phenomenon.

OVERDOSAGE

There is no clinical experience with massive overdosage. The largest overdose involved a young hospitalized adult patient who was not being treated with pergolide but who intentionally took 60 mg of the drug. He experienced vomiting, hypotension, and agitation. Another patient receiving a daily dosage of 7 mg of pergolide unintentionally took 19 mg/day for 3 days, after which his vital signs were normal but he experienced severe hallucinations. Within 36 hours of resumption of the prescribed dosage level, the hallucinations stopped. One patient unintentionally took 14 mg/day for 23 days instead of her prescribed 1.4 mg/day dosage. She experienced severe involuntary movements and tingling in her arms and legs. Another patient who inadvertently received 7 mg instead of the prescribed 0.7 mg experienced palpitations, hypotension, and ventricular extrasystoles. The highest total daily dose (prescribed for several patients with refractory Parkinson's disease) has exceeded 30 mg.

Symptoms — Animal studies indicate that the manifestations of overdosage in man might include nausea, vomiting, convulsions, decreased blood pressure, and CNS stimulation. The oral median lethal doses in mice and rats were 54 and 15 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference* (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Management of overdosage may require supportive measures to maintain arterial blood pressure. Cardiac function should be monitored; an antiarrhythmic agent may be necessary. If signs of CNS stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdose has not been assessed.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

There is no experience with dialysis or hemoperfusion, and these procedures are unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

Administration of Permax should be initiated with a daily dosage of 0.05 mg for the first 2 days. The dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal therapeutic dosage is achieved.

Permax is usually administered in divided doses 3 times per day. During dosage titration, the dosage of concurrent *l*-dopa/carbidopa may be cautiously decreased.

In clinical studies, the mean therapeutic daily dosage of Permax was 3 mg/day. The average concurrent daily dosage of *l*-dopa/carbidopa (expressed as *l*-dopa) was approximately 650 mg/day. The efficacy of Permax at doses above 5 mg/day has not been systematically evaluated. Doses of pergolide above 5 mg/day are not recommended (*see* WARNINGS).

HOW SUPPLIED

Tablets (modified rectangle shape, scored):

0.05 mg, ivory, debossed with A 024, in bottles of 30 (UC5336) — NDC 0187-0839-01

0.25 mg, green, debossed with A 025, in bottles of 100 (UC5337) — NDC 0187-0840-02

1 mg, pink, debossed with A 026, in bottles of 100 (UC5338) — NDC 0187-0841-02

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

PERMAX is a registered trademark of Eli Lilly and Company, and licensed in the US to Valeant Pharmaceuticals North America.

Manufactured for:

TASMAR®
(tolcapone)
TABLETS ℞

Before prescribing TASMAR, the physician should be thoroughly familiar with the details of this prescribing information.

TASMAR SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS AND THE PATIENT HAS PROVIDED WRITTEN ACKNOWLEDGEMENT THAT THE RISKS HAVE BEEN EXPLAINED (SEE PATIENT ACKNOWLEDGEMENT OF RISKS SECTION).

WARNING

Because of the risk of potentially fatal, acute fulminant liver failure, TASMAR (tolcapone) should ordinarily be used in patients with Parkinson's disease on l-dopa/carbidopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies (see INDICATIONS and DOSAGE AND ADMINISTRATION sections).

Because of the risk of liver injury and because TASMAR, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn from TASMAR.

TASMAR therapy should not be initiated if the patient exhibits clinical evidence of liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal. Patients with severe dyskinesia or dystonia should be treated with caution (see PRECAUTIONS: *Rhabdomyolysis*).

Patients who develop evidence of hepatocellular injury while on TASMAR and are withdrawn from the drug for any reason may be at increased risk for liver injury if TASMAR is reintroduced. Accordingly, such patients should not ordinarily be considered for retreatment.

Cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in postmarketing use. As of May 2005, 3 cases of fatal fulminant hepatic failure have been reported from more than 40,000 patient years of worldwide use. This incidence may be 10- to 100-fold higher than the background incidence in the general population. Underreporting of cases may lead to significant underestimation of the increased risk associated with the use of TASMAR. All 3 cases were reported within the first six months of initiation of treatment with TASMAR. Analysis of the laboratory monitoring data in over 3,400 TASMAR-treated patients participating in clinical trials indicated that increases in SGPT/ALT or SGOT/AST, when present, generally occurred within the first 6 months of treatment with TASMAR.

A prescriber who elects to use TASMAR in face of the increased risk of liver injury is strongly advised to monitor patients for evidence of emergent liver injury. Patients should be advised of the need for self-monitoring for both the classical signs of liver disease (e.g., clay colored stools, jaundice) and the nonspecific ones (e.g., fatigue, loss of appetite, lethargy).

Although a program of periodic laboratory monitoring for evidence of hepatocellular injury is recommended, it is not clear that periodic monitoring of liver enzymes will prevent the occurrence of fulminant liver failure. However, it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Accordingly, the following liver monitoring program is recommended.

Before starting treatment with TASMAR, the physician should conduct appropriate tests to exclude the presence of liver disease. In patients determined to be appropriate candidates for treatment with TASMAR, serum glutamic-pyruvic transaminase (SGPT/ALT) and serum glutamic-oxaloacetic transaminase (SGOT/AST) levels should be determined at baseline and periodically (i.e. every 2 to 4 weeks) for the first 6 months of therapy. After the first six months, periodic monitoring is recommended at intervals deemed clinically relevant. Although more frequent monitoring increases the chances of early detection, the precise schedule for monitoring is a matter of clinical judgement. If the dose is increased to 200 mg tid (see DOSAGE AND ADMINISTRATION section), liver enzyme monitoring should take place before increasing the dose and then be conducted every 2 to 4 weeks for the following 6 months of therapy. After six months, periodic monitoring is recommended at intervals deemed clinically relevant.

TASMAR should be discontinued if SGPT/ALT or SGOT/AST levels exceed 2 times the upper limit of normal or if clinical signs and symptoms suggest the onset of hepatic dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, and right upper quadrant tenderness).

or alterations of fluid and electrolyte bal-
ate hepatic coma.
iamterene has been reported in renal
tion with other calculus components.
be used with caution in patients with his-
iasis.
cy—Triamterene is a weak folic acid an-
contribute to the appearance of megalo-
ces where folic acid stores are decreased.
periodic blood evaluations are recom-

yperuricemia may occur or acute gout
ed in certain patients receiving thiazide

locrine Effects—The thiazides may de-
levels without signs of thyroid distur-

is decreased by thiazides. Pathological
athyroid gland with hypercalcemia and
have been observed in a few patients on
therapy. The common complications of
im such as renal lithiasis, bone resorp-
ceration have not been seen. Thiazides
ued before carrying out tests for parathy-

ts in diabetic patients may be increased,
nged. Diabetes mellitus which has been
manifest during thiazide administration.
lensitivity reactions to thiazides may
th or without a history of allergy or bron-

on or activation of systemic lupus ery-
zides has been reported.
-Thiazides may add to or potentiate the
hypertensive drugs.
ecrease arterial responsiveness to norep-
inution is not sufficient to preclude effec-
sor agent for therapeutic use. Thiazides
n to increase responsiveness to tubocura-

hould not be given with diuretics because
l clearance and add a high risk of lithium
e package insert on lithium before use of
herapy.
has been reported in a few patients re-
in and formulations containing triamte-
rothiazide. Caution is therefore advised
nonsteroidal anti-inflammatory agents
triamterene/hydrochlorothiazide.
gents should be used very cautiously, if
n with angiotensin-converting enzyme
e to a greatly increased risk of hypeka-
ium should be monitored frequently.
st Interactions—Triamterene and quini-
orescence spectra; thus MAXZIDE may
easurement of quinidine.
C—The safe use of MAXZIDE in preg-
stablished. Animal reproduction studies
ducted with MAXZIDE. It is also not
can cause fetal harm when adminis-
woman or can affect reproductive capac-
he placental barrier and appear in cord
azides in pregnant women requires that
fit be weighed against possible hazards
azards include fetal or neonatal jaun-
nia, pancreatitis, and possibly other
which have occurred in the adult.
e given to a pregnant woman only if

hiazides appear in breast milk. If the
eemed essential, the patient should stop

afety and effectiveness of MAXZIDE in
en established.

IONS

ed in association with the use of
iamterene/hydrochlorothiazide combi-
ude drowsiness and fatigue, insomnia,
weakness, headache, nausea, appetite
g, diarrhea, constipation, urine discol-
creased sexual performance, tachycar-
th and chest pain, dry mouth, depres-
e incidents of acute interstitial nephri-
lure have been reported. Other adverse
been reported with the individual ac-

Gastrointestinal: anorexia, gastric
jaundice (intrahepatic cholestatic
is, sialadenitis.
em: vertigo, paresthesias, xanthopsia.
nia, agranulocytosis, thrombocytope-
hemolytic anemia, megaloblastosis.
static hypotension (may be aggravated
es, or narcotics).

Hypersensitivity: anaphylaxis, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis.
Other: hyperglycemia, glycosuria, hyperuricemia, restlessness, transient blurred vision.
Triamterene:
Hypersensitivity: anaphylaxis, photosensitivity and rash.
Other: Triamterene has been reported in renal stones in association with other calculus materials. Triamterene has been associated with blood dyscrasias.
Whenever adverse reactions are moderate to severe, therapy should be reduced or withdrawn.

OVERDOSAGE

No specific data are available regarding MAXZIDE *triamterene/hydrochlorothiazide* overdosage in humans and no specific antidote is available.
Fluid and electrolyte imbalances are the most important concern. Excessive doses of the triamterene component may elicit hyperkalemia, dehydration, nausea, vomiting and weakness and possibly hypotension. Overdosing with hydrochlorothiazide has been associated with hypokalemia, hypochloremia, hyponatremia, dehydration, lethargy (may progress to coma) and gastrointestinal irritation. Treatment is symptomatic and supportive. Therapy with MAXZIDE should be discontinued. Induce emesis or institute gastric lavage. Monitor serum electrolyte levels and fluid balance. Institute supportive measures as required to maintain hydration, electrolyte balance, respiratory, cardiovascular and renal function.

DOSAGE AND ADMINISTRATION

The usual dose of MAXZIDE-25 MG is one or two tablets daily, given as a single dose, with appropriate monitoring of serum potassium (see **WARNINGS**). The usual dose of MAXZIDE is one tablet daily, with appropriate monitoring of serum potassium (see **WARNINGS**). There is no experience with the use of more than one MAXZIDE tablet daily or more than two MAXZIDE-25 MG tablets daily. Clinical experience with the administration of two MAXZIDE-25 MG tablets daily in divided doses (rather than as a single dose) suggests an increased risk of electrolyte imbalance and renal dysfunction.
Patients receiving 50 mg of hydrochlorothiazide who become hypokalemic may be transferred to MAXZIDE directly. Patients receiving 25 mg hydrochlorothiazide who become hypokalemic may be transferred to MAXZIDE-25 MG 37.5 mg triamterene/25 mg hydrochlorothiazide directly.
In patients requiring hydrochlorothiazide therapy and in whom hypokalemia cannot be risked, therapy may be initiated with MAXZIDE-25 MG. If an optimal blood pressure response is not obtained with MAXZIDE-25 MG, the dose should be increased to two MAXZIDE-25 MG tablets daily as a single dose, or one MAXZIDE tablet daily. If blood pressure still is not controlled, another antihypertensive agent may be added (see **PRECAUTIONS, Drug Interactions**).
Clinical studies have shown that patients taking less bioavailable formulations of triamterene and hydrochlorothiazide (totaling 75–100 mg hydrochlorothiazide and 150–200 mg triamterene) may be safely changed to one MAXZIDE tablet per day. Patients receiving less bioavailable formulations of triamterene and hydrochlorothiazide in daily doses of 25–50 mg hydrochlorothiazide and 50–100 mg triamterene may be safely changed to one MAXZIDE-25 MG tablet daily. All patients changed from less bioavailable formulations to MAXZIDE should be monitored clinically and for serum potassium after the transfer.

HOW SUPPLIED

MAXZIDE tablets are bowtie-shaped, flat-faced beveled, light yellow tablets, engraved with MAXZIDE on one side and scored on the other with LL on the left and M8 on the right of the score. Each tablet contains 75 mg of triamterene, USP and 50 mg of hydrochlorothiazide, USP. They are supplied as follows:
NDC 0005-4460-43—Bottle of 100 with CRC
NDC 0005-4460-31—Bottle of 500
NDC 0005-4460-60—Unit Dose 10 × 10s
MAXZIDE-25 MG tablets are bowtie-shaped, flat-faced beveled, light green tablets, engraved with MAXZIDE on one side and scored on the other with LL on the left and M9 on the right of the score. Each tablet contains 37.5 mg of triamterene, USP and 25 mg hydrochlorothiazide, USP.
They are supplied as follows:
NDC 0005-4464-43—Bottle of 100 with CRC
NDC 0005-4464-60—Unit Dose 10 × 10s
Store at Controlled Room Temperature 15–30°C (59–86°F).
Protect From Light.
Dispense in a tight, light-resistant, child-resistant container.
MILITARY and VA Depots:
MAXZIDE Triamterene 75 mg/Hydrochlorothiazide 50 mg
NSN 6505-01-196-5402—(100s)
NSN 6505-01-206-5068—(500s)
VA Depot:
NSN 6505-01-196-5403—Unit Dose (10 × 10s)
NSN 6505-01-223-8008—(30s)

(8/88)

Manufactured for
LEDERLE LABORATORIES DIVISION
American Cyanamid Company, Pearl River, NY 10965
by
MYLAN PHARMACEUTICALS, INC.
Morgantown, West Virginia 26505
Shown in Product Identification Section, page 414

METHOTREXATE Tablets ℞
METHOTREXATE Sodium ℞
METHOTREXATE LPF®Sodium Parenteral ℞

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDES THE USE OF ANTIMETABOLITE THERAPY.
THE USE OF METHOTREXATE HIGH-DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE (see DOSAGE AND ADMINISTRATION). HIGH-DOSAGE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.
BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS, THE PATIENT SHOULD BE INFORMED BY THE PHYSICIAN OF THE RISKS INVOLVED AND SHOULD BE UNDER A PHYSICIAN'S CONSTANT SUPERVISION.
DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY AND PSORIASIS.
IN THE TREATMENT OF PSORIASIS, METHOTREXATE USE SHOULD BE RESTRICTED TO PATIENTS WITH SEVERE RECALCITRANT, DISABLING DISEASE, WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY, AND ONLY WHEN THE DIAGNOSIS HAS BEEN ESTABLISHED AND AFTER APPROPRIATE CONSULTATION.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant patients with psoriasis should not receive methotrexate. (See PRECAUTIONS.)
2. A mandatory part of methotrexate therapy is periodic monitoring for toxicity, including CBC with differential and platelet counts, and liver and renal function tests. Periodic liver biopsies may be indicated in some situations. Patients at increased risk for higher blood levels of methotrexate should be monitored more frequently. (See PRECAUTIONS.)
3. Methotrexate can be hepatotoxic. Transient elevations of liver enzymes are seen frequently. Liver biopsies have shown fatty change and portal inflammation, and fibrosis and cirrhosis have been reported; these lesions may occur in the absence of symptoms or previous liver function test abnormalities. (See PRECAUTIONS.)
4. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy; it is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) require interruption of treatment and careful investigation.
5. Methotrexate may produce marked bone marrow depression, with resultant anemia, leukopenia, and/or thrombocytopenia.
6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Methotrexate therapy in patients with abnormal renal function should be undertaken, if at all, with extreme caution, and at reduced dosages, because renal impairment will elevate methotrexate blood levels.
8. Deaths have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See PRECAUTIONS.)

Continued on next page

Ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-di-chlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine.

CLINICAL PHARMACOLOGY

Tinea (pityriasis) versicolor is a non-contagious infection of the skin caused by *Pityrosporum orbiculare (Malassezia furfur)*. This commensal organism is part of the normal skin flora. In susceptible individuals the condition is often recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental skin exposure. The rate of recurrence of infection is variable.

When ketoconazole 2% shampoo was applied dermally to intact or abraded skin of rabbits for 28 days at doses up to 50 mg/kg and allowed to remain one hour before being washed away, there were no detectable plasma ketoconazole levels using an assay method having a lower detection limit of 5 ng/mL. NIZORAL® (ketoconazole) was not detected in plasma in 39 patients who shampooed 4–10 times per week for 6 months or in 33 patients who shampooed 2–3 times per week for 3–26 months (mean: 16 months).

An exaggerated use washing test on the sensitive antecubital skin of 10 subjects twice daily for five consecutive days showed that the irritancy potential of ketoconazole 2% shampoo was significantly less than that of 2.5% selenium sulfide shampoo.

A human sensitization test, a phototoxicity study, and a photoallergy study conducted in 38 male and 22 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no phototoxicity and no photoallergenic potential due to NIZORAL® (ketoconazole) 2% Shampoo.

Mode of Action: Interpretations of *in vivo* studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. It is postulated, but not proven, that the therapeutic effect of ketoconazole in tinea (pityriasis) versicolor is due to the reduction of *Pityrosporum orbiculare (Malassezia furfur)* and that the therapeutic effect in dandruff is due to the reduction of *Pityrosporum ovale*. Support for the therapeutic effect in tinea versicolor comes from a three-arm, parallel, double-blind, placebo-controlled study in patients who had moderately severe tinea (pityriasis) versicolor. Successful response rates in the primary efficacy population for each of both three-day and single-day regimens of ketoconazole 2% shampoo were statistically significantly greater (73% and 69%, respectively) than a placebo regimen (5%). There had been mycological confirmation of fungal disease in all cases at baseline. Mycological clearing rates were 84% and 78%, respectively, for the three-day and one-day regimens of the 2% shampoo and 11% in the placebo regimen. While the differences in the rates of successful response between either of the two active treatments and placebo were statistically significant, the difference between the two active regimens was not.

Microbiology: NIZORAL® (ketoconazole) is a broad-spectrum synthetic antifungal agent which inhibits the growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum* and *Epidermophyton floccosum;* yeasts: *Candida albicans, C. tropicalis, Pityrosporum ovale (Malassezia ovale)* and *Pityrosporum orbiculare (M. furfur)*. Development of resistance by these microorganisms to ketoconazole has not been reported.

INDICATIONS AND USAGE

NIZORAL® (ketoconazole) 2% Shampoo is indicated for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbiculare* (also known as *Malassezia furfur* or *M. orbiculare*).

Note: Tinea (pityriasis) versicolor may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in normalization of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental sun exposure. Although tinea versicolor is not contagious, it may recur because the organism that causes the disease is part of the normal skin flora.

CONTRAINDICATIONS

NIZORAL® (ketoconazole) 2% Shampoo is contraindicated in persons who have shown hypersensitivity to the active ingredient or excipients of this formulation.

PRECAUTIONS

General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

avoided.

There have been reports that use of the shampoo resulted in removal of the curl from permanently waved hair.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative. A long-term feeding study of ketoconazole in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

Pregnancy: Teratogenic effects: Pregnancy Category C: Ketoconazole is not detected in plasma after chronic shampooing. Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given orally in the diet at 80 mg/kg/day (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

There are no adequate and well-controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: Ketoconazole is not detected in plasma after chronic shampooing. Nevertheless, caution should be exercised when NIZORAL® (ketoconazole) 2% Shampoo is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In 11 double-blind trials in 264 patients using ketoconazole 2% shampoo for the treatment of dandruff or seborrheic dermatitis, an increase in normal hair loss and irritation occurred in less than 1% of patients. In three open-label safety trials in which 41 patients shampooed 4–10 times weekly for six months, the following adverse experiences each occurred once: abnormal hair texture, scalp pustules, mild dryness of the skin, and itching. As with other shampoos, oiliness and dryness of hair and scalp have been reported. In a double-blind, placebo-controlled trial in which patients with tinea versicolor were treated with either a single application of NIZORAL® (ketoconazole) 2% Shampoo (n=106), a daily application for three consecutive days (n=107), or placebo (n=105), drug-related adverse events occurred in 5 (5%), 7 (7%) and 4 (4%) of patients, respectively. The only events that occurred in more than one patient in any one of the three treatment groups were pruritus, application site reaction, and dry skin; none of these events occurred in more than 3% of the patients in any one of the three groups.

OVERDOSAGE

NIZORAL® (ketoconazole) 2% Shampoo is intended for external use only. In the event of accidental ingestion, supportive measures should be employed. Induced emesis and gastric lavage should usually be avoided.

DOSAGE AND ADMINISTRATION

Apply the shampoo to the damp skin of the affected area and a wide margin surrounding this area. Lather, leave in place for 5 minutes, and then rinse off with water.

One application of the shampoo should be sufficient.

HOW SUPPLIED

NIZORAL® (ketoconazole) 2% Shampoo is a red-orange liquid supplied in a 4-fluid ounce nonbreakable plastic bottle (NDC 50458-223-04).

Storage conditions: Store at a temperature not above 25°C (77°F). Protect from light.

Manufactured by:
Janssen Cilag SPA
Latina, Italy
Distributed by:
Janssen Pharmaceutica Inc.
Titusville, NJ 08560
Revised June 1996, August 1997
U.S. Patent No. 4,335,125

Shown in Product Identification Guide, page 317

NIZORAL® ℞
[nī 'zōr-ăl]
(ketoconazole)
Tablets

WARNING: When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See WARNINGS and PRECAUTIONS sections. Coadministration of terfenadine with ketoconazole tablets is contraindicated. Rare cases of serious cardiovas-

patients taking ketoconazole tablets
terfenadine, due to increased terfen
tions induced by ketoconazole tablets
DICATIONS, WARNINGS, and
sections.

Pharmacokinetic data indicate that
inhibits the metabolism of astemizole
vated plasma levels of astemizole and
olite desmethylastemizole which may
vals. Coadministration of astemizole
tablets is therefore contraindicated. See
CATIONS, WARNINGS, and PRECAUTIONS
Coadministration of cisapride with K
traindicated. Serious cardiovascular
cluding ventricular tachycardia, ventricular
and torsades de pointes have occurred
ing ketoconazole concomitantly with
CONTRAINDICATIONS, WARNINGS
TIONS sections.

DESCRIPTION

NIZORAL® (ketoconazole) is a synthetic
antifungal agent available in scored white
taining 200 mg ketoconazole base for oral
Inactive ingredients are colloidal silicon
starch, lactose, magnesium stearate, microcrystalline cellulose, and povidone. Ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxyl]phenyl] piperazine.
Ketoconazole is a white to slightly beige powder, soluble in acids, with a molecular weight of

CLINICAL PHARMACOLOGY

Mean peak plasma levels of approximately
reached within 1 to 2 hours, following oral
a single 200 mg dose taken with a meal. Subsequent elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, NIZORAL® is
is converted into several inactive metabolites. The
identified metabolic pathways are oxidation
tion of the imidazole and piperazine rings
dealkylation and aromatic hydroxylation. About
dose is excreted in the urine, of which 2 to 4%
drug. The major route of excretion is through
the intestinal tract. *In vitro*, the plasma protein
about 99% mainly to the albumin fraction. Only
proportion of ketoconazole reaches the cerebral
Ketoconazole is a weak dibasic agent and
acidity for dissolution and absorption.
NIZORAL® Tablets are active against clinical
with *Blastomyces dermatitidis, Candida spp.*, *Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis*, and *Phialophora spp.* NIZORAL® Tablets are active against *Trichophyton spp., Epidermophyton floccosum, Microsporum spp.* Ketoconazole is also active against a variety of fungi and yeast. In animal models activity has been demonstrated against *Candida albicans, Blastomyces dermatitidis, Histoplasma capsulatum, Pityrosporum furfur, Coccidioides immitis*, and *Cryptococcus neoformans*.
Mode of Action: In vitro studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes.

INDICATIONS AND USAGE

NIZORAL® (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral candidiuria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL® Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebral spinal fluid. NIZORAL® Tablets are also indicated for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy, griseofulvin, or who are unable to take griseofulvin.

CONTRAINDICATIONS

Coadministration of terfenadine or astemizole with ketoconazole tablets is contraindicated. (See BOX WARNING, WARNINGS, and PRECAUTIONS sections.)
Concomitant administration of NIZORAL® Tablets and cisapride is contraindicated. (See BOX WARNING, WARNINGS, and PRECAUTIONS sections.)
Concomitant administration of NIZORAL® Tablets and oral triazolam is contraindicated. (See PRECAUTIONS section.)
NIZORAL® is contraindicated in patients who have hypersensitivity to the drug.

1. **Treatment of Hypercalcemia and Overdosage in Patients on Hemodialysis**
General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of normal range) consists of immediate discontinuation of Calcijex® therapy, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until normocalcemia ensues. Hypercalcemia usually resolves in two to seven days. When serum calcium levels have returned to within normal limits, Calcijex® therapy may be reinstituted at a dose 0.5 mcg less than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes.
Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.
2. **Treatment of Accidental Overdosage of Calcitriol Injection**
The treatment of acute accidental overdosage of Calcijex® should consist of general supportive measures. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdosage. Due to the relatively short duration of the pharmacological action of calcitriol, further measures are probably unnecessary. Should, however, persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered, depending on the patients' underlying condition. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. The use of peritoneal dialysis against a calcium-free dialysate has also been reported.

DOSAGE AND ADMINISTRATION

The optimal dose of Calcijex® (calcitriol injection) must be carefully determined for each patient.
The effectiveness of Calcijex® therapy is predicated on the assumption that each patient is receiving an adequate and appropriate daily intake of calcium. The RDA for calcium in adults is 800 mg. To ensure that each patient receives an adequate daily intake of calcium, the physician should either prescribe a calcium supplement or instruct the patient in proper dietary measures.
The recommended initial dose of Calcijex®, depending on the severity of the hypocalcemia and/or secondary hyperparathyroidism, is 1 mcg (0.02 mcg/kg) to 2 mcg administered three times weekly, approximately every other day. Doses as small as 0.5 mcg and as large as 4 mcg three times weekly have been used as an initial dose. If a satisfactory response is not observed, the dose may be increased by 0.5 to 1 mcg at two to four week intervals. During this titration period, serum calcium and phosphorus levels should be obtained at least twice weekly. If hypercalcemia or a serum calcium times phosphate product greater than 70 is noted, the drug should be immediately discontinued until these parameters are appropriate. Then, the Calcijex® dose should be reinitiated at a lower dose. Doses may need to be reduced as the PTH levels decrease in response to the therapy. Thus, incremental dosing must be individualized and commensurate with PTH, serum calcium and phosphorus levels. The following is a suggested approach in dose titration:

PTH Levels	Calcijex® Dose
the same or increasing	increase
decreasing by <30%	increase
decreasing by > 30%, < 60%	maintain
decreasing by > 60%	decrease
one and one-half to three times the upper limit of normal	maintain

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Discard unused portion.

HOW SUPPLIED

Calcijex® (calcitriol injection) is supplied as follows:

List	Container	Concentration	Fill
8110	Ampul	1 mcg/mL	1 mL

Protect from light.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Patent Pending.
Ref. EN-0249 Rev. September, 2004

Mfd.by:
Hospira, Rx, Lake Forest, IL 60045 USA
For ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064 USA

DEPAKOTE® ER

[dĕp' ă-kōte]
(divalproex sodium)
extended-release tablets

BOX WARNING

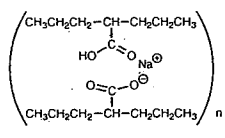
HEPATOTOXICITY
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.
THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

TERATOGENICITY
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA). ACCORDINGLY, THE USE OF DEPAKOTE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.
AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.

PANCREATITIS
CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See **WARNINGS** and **PRECAUTIONS.**)

DESCRIPTION

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium occurs as a white powder with a characteristic odor.
DEPAKOTE ER 250 and 500 mg tablets are for oral administration. DEPAKOTE ER tablets contain divalproex sodium in a once-a-day extended-release formulation equivalent to 250 and 500 mg of valproic acid.
Inactive Ingredients
DEPAKOTE ER 250 and 500 mg tablets: FD&C Blue No. 1, hypromellose, lactose, microcrystalline cellulose, polyethylene glycol, potassium sorbate, propylene glycol, silicon dioxide, titanium dioxide, and triacetin.
In addition, 500 mg tablets contain iron oxide and polydextrose.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).
Pharmacokinetics
Absorption/Bioavailability
The absolute bioavailability of DEPAKOTE ER tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion.
When given in equal total daily doses, the bioavailability of DEPAKOTE ER is less than that of DEPAKOTE (divalproex sodium delayed-release tablets). In five multiple-dose studies in healthy subjects (N=82) and in subjects with epilepsy (N=86), when administered under fasting and nonfasting conditions, DEPAKOTE ER given once daily produced an average bioavailability of 89% relative to an equal total daily dose of DEPAKOTE given BID, TID, or QID. The median time to maximum plasma valproate concentrations (C_{max}) after DEPAKOTE ER administration ranged from 4 to 17 hours. After multiple once-daily dosing of DEPAKOTE ER, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular DEPAKOTE given BID, TID, or QID.
Conversion from DEPAKOTE to DEPAKOTE ER
When DEPAKOTE ER is given in doses 8 to 20% higher than the total daily dose of DEPAKOTE, the two formulations are bioequivalent. In two randomized, crossover studies, multiple daily doses of DEPAKOTE were compared to 8 to 20% higher once-daily doses of DEPAKOTE ER. In these two studies, DEPAKOTE ER and DEPAKOTE regimens were equivalent with respect to area under the curve (AUC; a measure of the extent of bioavailability). Additionally, valproate C_{max} was lower, and C_{min} was either higher or not different, for DEPAKOTE ER relative to DEPAKOTE regimens (see following table).
[See table at top of next page]
Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepine, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when converting between DEPAKOTE and DEPAKOTE ER.
Distribution
Protein Binding
The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 µg/mL to 18.5% at 130 µg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide) (see **PRECAUTIONS - Drug Interactions** for more detailed information on the pharmacokinetic interactions of valproate with other drugs).
CNS Distribution
Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).
Metabolism
Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.
The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.
Elimination
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg.
The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbi-

Zemplar Injection—Cont.

REFERENCES
1. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003; Volume 42(4): Supplement 3.

Ref: EN-0958 (09/05)
Revised: September, 2005
Manufactured by
Hospira, Inc.
Lake Forest, IL 60045 USA
For
Abbott Laboratories
North Chicago, IL 60064, U.S.A.

Information on the Abbott pharmaceutical products listed on these pages is from the prescribing information in use as of June 1, 2007. For more information, please visit rxabbott.com or call 1-800-633-9110.

Actelion Pharmaceuticals US, Inc.

5000 SHORELINE COURT, SUITE 200
S. SAN FRANCISCO, CA 94080

Direct Inquiries to:
Actelion Medical Information
866-228-3546
(follow the prompts)

TRACLEER®

℞

[trŏk' lēr]

bosentan tablets

62.5 mg and 125 mg film-coated tablets

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury

TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with TRACLEER® in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of TRACLEER® in these cases could not be excluded.

In at least one case the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of TRACLEER®. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping TRACLEER® with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction (see DOSAGE AND ADMINISTRATION).

Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION).

TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 × ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 × ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy

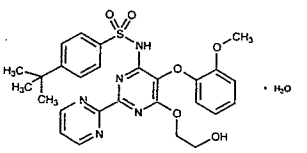
TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions). Therefore, effective contraception through additional forms of contraception must be practiced. Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through the TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

DESCRIPTION

Bosentan is the first of a new drug class, an endothelin receptor antagonist.

TRACLEER® (bosentan) belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxy-phenoxy)-[2,2']-bipyrimidin-4-yl]-benzenesulfonamide monohydrate and has the following structural formula:



Bosentan has a molecular weight of 569.64 and a molecular formula of $C_{27}H_{29}N_5O_6S \cdot H_2O$. Bosentan is a white to yellowish powder. It is poorly soluble in water (1.0 mg/100 mL) and in aqueous solutions at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0). Solubility increases at higher pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive.

TRACLEER® is available as 62.5 mg and 125 mg film-coated tablets for oral administration, and contains the following excipients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, and ethylcellulose. Each TRACLEER® 62.5 mg tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan. Each TRACLEER® 125 mg tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.

CLINICAL PHARMACOLOGY

Mechanism of Action

Endothelin-1(ET-1)is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors.

Pharmacokinetics

General

After oral administration, maximum plasma concentrations of bosentan are attained within 3–5 hours and the terminal elimination half-life (t½) is about 5 hours in healthy adult subjects. The exposure to bosentan after intravenous and oral administration is about 2-fold greater in adult patients with pulmonary arterial hypertension than in healthy adult subjects.

Absorption and Distribution

The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. The volume of distribution is about 18 L. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Metabolism and Elimination

Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%–20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Total clearance after a single intravenous dose is about 4 L/hr in patients with pulmonary arterial hypertension. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50–65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3–5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine.

Special Populations

It is not known whether bosentan's pharmacokinetics is influenced by gender, body weight, race, or age.

Liver Function Impairment

In vitro and in vivo evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (as indicated by the Child-Pugh method) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan were not altered in patients with mild hepatic impairment. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. Bosentan should generally be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases >3 × ULN (See **DOSAGE AND ADMINISTRATION** and **WARNINGS**).

Renal Impairment

In patients with severe renal impairment (creatinine clearance 15–30 mL/min), plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important (See **DOSAGE AND ADMINISTRATION**).

Clinical Studies

Pulmonary Arterial Hypertension

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1) compared 2 doses (125 mg b.i.d.and 250 mg b.i.d.) of TRACLEER® with placebo. The smaller study (Study 351) compared 125 mg b.i.d. with placebo. Patients had severe (WHO functional Class III–IV) pulmonary arterial hypertension: primary pulmonary hypertension (72%) or pulmonary hypertension secondary to scleroderma or other connective tissue diseases (21%), or to autoimmune diseases (7%). There were no patients with pulmonary hypertension secondary to other conditions such as HIV disease, or recurrent pulmonary emboli.

In both studies, TRACLEER® or placebo was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators (e.g., calcium channel blockers, ACE inhibitors), but not epoprostenol. TRACLEER® was given at a dose of 62.5 mg b.i.d. for 4 weeks and then at 125 mg b.i.d. or 250 mg b.i.d. for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study endpoint was 6-minute walk distance. In addition, symptoms and functional status were assessed. Hemodynamic measurements were made at 12 weeks in Study 351.

The mean age was about 49 years. About 80% of patients were female, and about 80% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

Submaximal Exercise Capacity

Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in Table 1.

[See table 1 below]

In both trials, treatment with TRACLEER® resulted in a significant increase in exercise capacity. The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg b.i.d.) and fully developed by about 2 months of treatment (Figure 1). It was maintained for up to 7 months of double-blind treatment. Walking distance was somewhat greater with 250 mg b.i.d., but the potential for increased liver injury causes this dose not to be recommended (See **DOSAGE AND ADMINISTRATION**). There were no apparent differences in treatment effects on walk distance among subgroups analyzed by demographic fac-

Table 1. Effects of bosentan on 6-minute walk distance

	BREATHE-1			Study 351	
	Bosentan 125 mg b.i.d. (n = 74)	*Bosentan 250 mg b.i.d. (n = 70)*	Placebo (n = 69)	Bosentan 125 mg b.i.d. (n = 21)	Placebo (n = 11)
Baseline	*326 ± 73*	*333 ± 75*	344 ± 76	360 ± 86	355 ± 82
End point	*353 ± 115*	*379 ± 101*	336 ± 129	431 ± 66	350 ± 147
Change from baseline	*27 ± 75*	*46 ± 62*	-8 ± 96	70 ± 56	-6 ± 121
Placebo – subtracted	*35*[a]	*54*[b]		76[c]	

Distance in meters: mean ± standard deviation. Changes are to week 16 for BREATHE-1 and to week 12 for Study 351.
[a] p = 0.01; by Wilcoxon
[b] p = 0.0001 for 250 mg; by Wilcoxon
[c] p = 0.02; by Student's t-test.

Amevive—Cont.

Malignancies

In the 24-week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 AMEVIVE®-treated patients. The incidence of malignancies was 1.3% (11/876) for AMEVIVE®-treated patients compared to 0.5% (2/413) in the placebo group.

Among 1869 patients who received AMEVIVE® at any dose in clinical trials, 43 patients were diagnosed with 63 treatment-emergent malignancies. The majority of the malignancies were non-melanoma skin cancers: 46 cases (20 basal cell, 26 squamous cell carcinomas) in 27 patients. Other malignancies observed in AMEVIVE®-treated patients included melanoma (n=3), solid organ malignancies (n=12 in 11 patients), and lymphomas (n=5); the latter consisted of two Hodgkin's and two non-Hodgkin's lymphomas, and one cutaneous T cell lymphoma (mycosis fungoides).

Infections

In the 24-week period constituting the first course of placebo-controlled studies, serious infections (infections requiring hospitalization) were seen at a rate of 0.9% (8/876) in AMEVIVE®-treated patients and 0.2% (1/413) in the placebo group. In patients receiving repeated courses of AMEVIVE® therapy, the rates of serious infections remained similar across courses of therapy. Serious infections among 1869 AMEVIVE®-treated patients included cellulitis, abscesses, wound infections, toxic shock, pneumonia, appendicitis, cholecystitis, gastroenteritis and herpes infections.

Hypersensitivity Reactions

In clinical studies, 4 of 1869 (0.2%) patients were reported to experience angioedema: two of these patients were hospitalized. In the 24-week period constituting the first course of placebo-controlled studies, urticaria was reported in 6 (<1%) AMEVIVE®-treated patients *vs.* 1 patient in the control group. Urticaria resulted in discontinuation of therapy in one of the AMEVIVE®-treated patients.

Hepatic Injury

In post-marketing experience there have been reports of asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis, and severe liver failure (see **PRECAUTIONS, hepatic injury**).

In the 24-week period constituting the first course of placebo-controlled studies, 1.7% (15/876) of AMEVIVE®-treated patients and 1.2% (5/413) of the placebo group experienced ALT and/or AST elevations of at least 3 times the upper limit of normal.

Injection Site Reactions

In the intramuscular study (Study 2), 16% of AMEVIVE®-treated patients and 8% of placebo-treated patients reported injection site reactions. In patients receiving repeated courses of AMEVIVE® IM therapy, the incidence of injection site reactions remained similar across courses of therapy. Reactions at the site of injection were generally mild, typically occurred on single occasions, and included either pain (7%), inflammation (4%), bleeding (4%), edema (2%), non-specific reaction (2%), mass (1%), or skin hypersensitivity (<1%). In the clinical trials, a single case of injection site reaction led to the discontinuation of AMEVIVE®.

Immunogenicity

Approximately 3% (40/1357) of patients receiving AMEVIVE® developed low-titer antibodies to alefacept. No apparent correlation of antibody development and clinical response or adverse events was observed. The long-term immunogenicity of AMEVIVE® is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to alefacept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alefacept with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

The highest dose tested in humans (0.75 mg/kg IV) was associated with chills, headache, arthralgia, and sinusitis within one day of dosing. Patients who have been inadvertently administered an excess of the recommended dose should be closely monitored for effects on total lymphocyte count and CD4+ T lymphocyte count.

DOSAGE AND ADMINISTRATION

AMEVIVE® should only be used under the guidance and supervision of a physician.

The recommended dose of AMEVIVE® is 7.5 mg given once weekly as an IV bolus or 15 mg given once weekly as an IM injection. The recommended regimen is a course of 12 weekly injections. Retreatment with an additional 12-week course may be initiated provided that CD4+ T lymphocyte counts are within the normal range, and a minimum of a 12-week interval has passed since the previous course of treatment.

The CD4+ T lymphocyte counts of patients receiving AMEVIVE® should be monitored before initiating dosing and every two weeks throughout the course of the 12-week dosing regimen. If CD4+ T lymphocyte counts are below 250 cells/μL, AMEVIVE® dosing should be withheld and weekly monitoring instituted. AMEVIVE® should be discontinued if the counts remain below 250 cells/μL for one month (see **PRECAUTIONS, Laboratory Tests**).

Preparation Instructions

AMEVIVE® should be reconstituted by a health care professional using aseptic technique. Each vial is intended for single patient use only.

Do not use AMEVIVE® beyond the date stamped on the carton, dose pack lid (IV), drug/diluent pack (IM), AMEVIVE® vial label, or diluent container label.

AMEVIVE® 15 mg lyophilized powder for IM administration should be reconstituted with 0.6 mL of the supplied diluent (Sterile Water for Injection, USP). 0.5 mL of the reconstituted solution contains 15 mg of alefacept.

AMEVIVE® 7.5 mg lyophilized powder for IV administration should be reconstituted with 0.6 mL of the supplied diluent. 0.5 mL of the reconstituted solution contains 7.5 mg of alefacept.

Do not add other medications to solutions containing AMEVIVE®. Do not reconstitute AMEVIVE® with other diluents. Do not filter reconstituted solution during preparation or administration.

All procedures require the use of aseptic technique. Using the supplied syringe and one of the supplied needles, withdraw **only 0.6 mL** of the supplied diluent, (Sterile Water for Injection, USP). Keeping the needle pointed at the sidewall of the vial, slowly inject the diluent into the vial of AMEVIVE®. Some foaming will occur, which is normal. To avoid excessive foaming, do not shake or vigorously agitate. The contents should be swirled gently during dissolution. Generally, dissolution of AMEVIVE® takes less than two minutes. The solution should be used as soon as possible after reconstitution.

The reconstituted solution should be clear and colorless to slightly yellow. Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if undissolved material remains.

Following reconstitution, the product should be used immediately or within 4 hours if stored in the vial at 2-8°C (36-46°F). AMEVIVE® NOT USED WITHIN 4 HOURS OF RECONSTITUTION SHOULD BE DISCARDED.

Remove the needle used for reconstitution and attach the other supplied needle. Withdraw 0.5 mL of the AMEVIVE® solution into the syringe. Some foam or bubbles may remain in the vial.

Administration Instructions

For intramuscular use, inject the full 0.5 mL of solution. Rotate injection sites so that a different site is used for each new injection. New injections should be given at least 1 inch from an old site and never into areas where the skin is tender, bruised, red, or hard.

For intravenous use,

- Prepare 2 syringes with 3.0 mL Normal Saline, USP for pre- and post-administration flush.
- Prime the winged infusion set with 3.0 mL saline and insert the set into the vein.
- Attach the AMEVIVE®-filled syringe to the infusion set and administer the solution over no more than 5 seconds.
- Flush the infusion set with 3.0 mL saline, USP.

HOW SUPPLIED

[See table above]

AMEVIVE® for IV administration is supplied in either a carton containing four administration dose packs, or in a carton containing one administration dose pack. Each dose pack contains one 7.5-mg single-use vial of AMEVIVE®, one 10 mL single-use diluent vial (Sterile Water for Injection, USP), one syringe, one 23 gauge, ¾ inch winged infusion set, and two 23 gauge, 1 ¼ inch needles. The NDC number for the four administration dose pack carton is 0469-0020-01. The NDC number for the one administration dose pack carton is 0469-020-02.

AMEVIVE® for IM administration is supplied in either a carton containing four doses, or in a carton containing one dose. Each four-dose carton contains one removable drug/diluent pack for refrigeration, four 1 mL syringes, and eight 23 gauge, 1 ¼ inch needles. Each four-dose drug/diluent pack for refrigeration contains: four 15-mg single-use vials of AMEVIVE® and four 10 mL single-use diluent vials of Sterile Water for Injection, USP. Each single-dose carton contains one removable drug/diluent pack for refrigeration, one syringe and two 23 gauge, 1 ¼ inch needles. Each single-dose drug/diluent pack for refrigeration contains: one 15-mg single-use vial of AMEVIVE® and one 10 mL single-use diluent vial of Sterile Water for Injection, USP. The NDC number for the four-dose carton is 0469-0021-03. The NDC number for the single-dose carton is 0469-0021-04.

#	Name	Strength	Dosage Form	Appearance	Package Type	Package Qty	NDC
1	AMEVIVE	15	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (C42957)		CARTON (C43182)	1	0469-0021-04
1	AMEVIVE	15	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (C42957)		CARTON (C43182)	4	0469-0021-03
2	AMEVIVE	7.5	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (C42957)		CARTON (C43182)	1	0469 0020-02
2	AMEVIVE	7.5	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (C42957)		CARTON (C43182)	4	0469-0020-01

AMEVIVE® is reconstituted with 0.6 mL of the 10 mL single-use diluent.

Storage

The dose pack (IV) and drug/diluent pack (IM) containing AMEVIVE® (lyophilized powder) should be stored in a refrigerator between 2-8°C/36-46°F. PROTECT FROM LIGHT. Retain in carton (IV) or drug/diluent pack (IM) until time of use.

Rx only

REFERENCES

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2. Ellis C, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001; 345:248-255.

3. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica 1978; 157:238-244.

Revised: October 2006

AMEVIVE® (alefacept)

Manufactured by:

Astellas Pharma US, Inc.

Deerfield, IL 60015

US License # 1748

1-866-263-8483

U.S. Patents:

4,956,281

5,547,853

5,728,677

5,914,111

5,928,643

6,162,432

Additional U.S. Patents Pending

I63007-6

MYCAMINE®

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[mī-kă-mēn]

(micafungin sodium) For Injection

INTRAVENOUS INFUSION (not for IV bolus injection)

DESCRIPTION

Proprietary name:	MYCAMINE
Established name:	(micafungin sodium) for injection
Route of administration:	INTRAVENOUS (C38276)
Active ingredients (moiety):	micafungin sodium

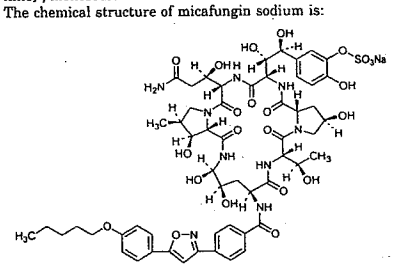
[See first table at top of next page]

MYCAMINE is a sterile, lyophilized product for intravenous (IV) infusion that contains micafungin sodium. Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1, 3-β-D-glucan, an integral component of the fungal cell wall.

Each single-use vial contains 50 mg or 100 mg micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment). MYCAMINE must be diluted with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (see **DOSAGE AND ADMINISTRATION**). Following reconstitution with 0.9% Sodium Chloride Injection, USP, the resulting pH of the solution is between 5.0-7.0.

Micafungin sodium is chemically designated as: Pneumocandin A0,1-[(4*R*,5*R*)-4,5-dihydroxy-*N*^{2}-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt.

The chemical structure of micafungin sodium is:



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#	Strength	Form	Inactive ingredients
1	50	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (C42957)	lactose, citric acid, sodium hydroxide
2	100	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (C42957)	lactose, citric acid, sodium hydroxide

[See figure at top of next column]

The empirical/molecular formula is $C_{56}H_{70}N_8NaO_{23}S$ and the formula weight is 1292.26.

Micafungin sodium is a light-sensitive, hygroscopic white powder that is freely soluble in water, isotonic sodium chloride solution, *N,N*-dimethylformamide and dimethylsulfoxide, slightly soluble in methyl alcohol, and practically insoluble in acetonitrile, ethyl alcohol (95%), acetone, diethyl ether and *n*-hexane.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of micafungin were determined in healthy subjects, hematopoietic stem cell transplant recipients, and patients with esophageal candidiasis up to a maximum daily dose of 8 mg/kg body weight.

The relationship of area under the concentration-time curve (AUC) to micafungin dose was linear over the daily dose range of 50 mg to 150 mg and 3 mg/kg to 8 mg/kg body weight.

Steady-state pharmacokinetic parameters in relevant patient populations after repeated daily administration are presented in the table below.

[See table 1 above]

Distribution

The mean ± standard deviation volume of distribution of micafungin at terminal phase was 0.39 ± 0.11 L/kg body weight when determined in adult patients with esophageal candidiasis at the dose range of 50 mg to 150 mg.

Micafungin is highly (>99%) protein bound *in vitro*, independent of plasma concentrations over the range of 10 to 100 mcg/mL. The primary binding protein is albumin; however, micafungin, at therapeutically relevant concentrations, does not competitively displace bilirubin binding to albumin. Micafungin also binds to a lesser extent to α_1-acid-glycoprotein.

Metabolism

Micafungin is metabolized to M-1 (catechol form) by arylsulfatase, with further metabolism to M-2 (methoxy form) by catechol-*O*-methyltransferase. M-5 is formed by hydroxylation at the side chain (ω-1 position) of micafungin catalyzed by cytochrome P450 (CYP) isozymes. Even though micafungin is a substrate for and a weak inhibitor of CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*. Micafungin is neither a P-glycoprotein substrate nor inhibitor *in vitro*.

In four healthy volunteer studies, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 6% for M-1, 1% for M-2, and 6% for M-5. In patients with esophageal candidiasis, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 11% for M-1, 2% for M-2, and 12% for M-5.

Excretion

The excretion of radioactivity following a single intravenous dose of ^{14}C-micafungin sodium for injection (25 mg) was evaluated in healthy volunteers. At 28 days after administration, mean urinary and fecal recovery of total radioactivity accounted for 82.5% (76.4 to 87.9%) of the administered dose. Fecal excretion is the major route of elimination (total radioactivity at 28 days was 71.0% of the administered dose).

Special Populations

MYCAMINE disposition has been studied in a variety of populations as described below.

Race And Gender

No dose adjustment of MYCAMINE is required based on gender or race. After 14 daily doses of 150 mg to healthy subjects, micafungin AUC in women was greater by approximately 23% compared with men, due to smaller body weight. No notable differences among white, black, and Hispanic subjects were seen. The micafungin AUC was greater by 26% in Japanese subjects compared to blacks, due to smaller body weight.

Renal Insufficiency

MYCAMINE does not require dose adjustment in patients with renal impairment.

A single 1-hour infusion of 100 mg MYCAMINE was administered to 9 subjects with severe renal dysfunction (creatinine clearance <30 mL/min) and to 9 age-, gender-, and weight-matched subjects with normal renal function (creatinine clearance >80 mL/min). The maximum concentration (C_{max}) and AUC were not significantly altered by severe renal impairment.

Since micafungin is highly protein bound, it is not dialyzable. Supplementary dosing should not be required following hemodialysis.

Hepatic Insufficiency

A single 1-hour infusion of 100 mg MYCAMINE was administered to 8 subjects with moderate hepatic dysfunction (Child-Pugh score 7-9) and 8 age-, gender-, and weight-matched subjects with normal hepatic function. The C_{max} and AUC values of micafungin were lower by approximately 22% in subjects with moderate hepatic insufficiency. This difference in micafungin exposure does not require dose adjustment of MYCAMINE in patients with moderate hepatic impairment. The pharmacokinetics of MYCAMINE have not been studied in patients with severe hepatic insufficiency.

Geriatric

The exposure and disposition of a 50 mg MYCAMINE dose administered as a single 1-hour infusion to 10 healthy subjects aged 66-78 years were not significantly different from those in 10 healthy subjects aged 20-24 years. No dose adjustment is necessary for the elderly.

Table 1: Pharmacokinetic Parameters of Micafungin in Adult Patients

Population	N	Dose (mg)	Pharmacokinetic Parameters (Mean ± Standard Deviation) C_{max} (mcg/mL)	AUC_{0-24} (mcg·h/mL)	$t_{1/2}$ (h)	Cl (mL/min/kg)
HIV*-Positive	20	50	5.1±1.0	54±13	15.6±2.8	0.300±0.063
Patients with EC†	20	100	10.1±2.6	115±25	16.9±4.4	0.301±0.086
[Day 14 or 21]	14	150	16.4±6.5	167±40	15.2±2.2	0.297±0.081
		per kg				
	8	3	21.1±2.84	234±34	14.0±1.4	0.214±0.031
HSCT‡ Recipients	10	4	29.2±6.2	339±72	14.2±3.2	0.204±0.036
[Day 7]	8	6	38.4±6.9	479±157	14.9±2.6	0.224±0.064
	8	8	60.8±26.9	663±212	17.2±2.3	0.223±0.081

* HIV=human immunodeficiency virus
† EC = esophageal candidiasis
‡ HSCT = hematopoietic stem cell transplant

MICROBIOLOGY

Mechanism Of Action

Micafungin, the active ingredient in MYCAMINE, inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls, which is not present in mammalian cells.

Activity *In Vitro*

Micafungin exhibited *in-vitro* activity against *C. albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis.* Standardized susceptibility testing methods for 1,3-β-D-glucan synthesis inhibitors have not been established, and the results of susceptibility studies do not correlate with clinical outcome.

Activity *In Vivo*

Micafungin sodium has shown activity in both mucosal and disseminated murine models of candidiasis. Micafungin sodium, administered to immunosuppressed mice in models of disseminated candidiasis prolonged survival and/or decreased the mycological burden.

Drug Resistance

The potential for development of drug resistance is not known.

INDICATIONS AND USAGE

MYCAMINE is indicated for:

- Treatment of patients with esophageal candidiasis (see **CLINICAL STUDIES, MICROBIOLOGY**).
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (see **CLINICAL STUDIES, MICROBIOLOGY**).

NOTE: The efficacy of MYCAMINE against infections caused by fungi other than *Candida* has not been established.

CONTRAINDICATIONS

MYCAMINE is contraindicated in patients with hypersensitivity to any component of this product.

WARNINGS

Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving MYCAMINE. If these reactions occur, MYCAMINE infusion should be discontinued and appropriate treatment administered.

PRECAUTIONS

Hepatic Effects

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with MYCAMINE. In some patients with serious underlying conditions who were receiving MYCAMINE along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported. Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing MYCAMINE therapy.

Renal Effects

Elevations in BUN and creatinine, and isolated cases of significant renal dysfunction or acute renal failure have been reported in patients who received MYCAMINE. In controlled trials, the incidence of drug-related renal adverse events was 0.4% for MYCAMINE treated patients and 0.5% for fluconazole treated patients. Patients who develop abnormal renal function tests during MYCAMINE therapy should be monitored for evidence of worsening renal function.

Hematological Effects

Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of MYCAMINE (200 mg) and oral prednisolone (20 mg). This event was transient, and the subject did not develop significant anemia. Isolated cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with MYCAMINE. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during MYCAMINE therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing MYCAMINE therapy.

Drug Interactions

A total of 11 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between MYCAMINE and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed.

There was no effect of a single dose or multiple doses of MYCAMINE on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state MYCAMINE compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state MYCAMINE compared with nifedipine alone. Patients receiving sirolimus or nifedipine in combination with MYCAMINE should be monitored for sirolimus or nifedipine toxicity and sirolimus or nifedipine dosage should be reduced if necessary.

Micafungin is not an inhibitor of P-glycoprotein and, therefore, would not be expected to alter P-glycoprotein-mediated drug transport activity.

Carcinogenesis, Mutagenesis And Impairment Of Fertility

No life-time studies in animals were performed to evaluate the carcinogenic potential of MYCAMINE. Micafungin sodium was not mutagenic or clastogenic when evaluated in a standard battery of *in-vitro* and *in-vivo* tests (i.e., bacterial reversion - *S. typhimurium, E. coli*; chromosomal aberration; intravenous mouse micronucleus).

Male rats treated intravenously with micafungin sodium for 9 weeks showed vacuolation of the epididymal ductal epithelial cells at or above 10 mg/kg (about 0.6 times the recommended clinical dose for esophageal candidiasis, based on body surface area comparisons). Higher doses (about twice the recommended clinical dose, based on body surface area comparisons) resulted in higher epididymis weights and reduced numbers of sperm cells. In a 39-week intravenous study in dogs, seminiferous tubular atrophy and decreased sperm in the epididymis were observed at 10 and 32 mg/kg, doses equal to about 2 and 7 times the recommended clinical dose, based on body surface area comparisons. There was no impairment of fertility in animal studies with micafungin sodium.

Pregnancy Category C

Micafungin sodium administration to pregnant rabbits (intravenous dosing on days 6 to 18 of gestation) resulted in visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to about four times the recommended dose based on body surface area comparisons. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter.

However, adequate, well-controlled studies were not conducted in pregnant women. Animal studies are not always predictive of human response; therefore, MYCAMINE should be used during pregnancy only if clearly needed.

Nursing Mothers

Micafungin was found in the milk of lactating, drug-treated rats. It is not known whether micafungin is excreted in human milk. Caution should be exercised when MYCAMINE is administered to a nursing woman.

Pediatric Use

The safety and efficacy of MYCAMINE in pediatric patients has not been established in clinical studies.

Geriatric Use

A total of 186 subjects in clinical studies of MYCAMINE were 65 years of age and older, and 41 subjects were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not

Continued on next page

Table 10

Body System Adverse Event[a]	Number (%) of Subjects ARIMIDEX (N=506)	Tamoxifen (N=511)	Body System Adverse Event[a]	Number (%) of Subjects ARIMIDEX (N=506)	Tamoxifen (N=511)
Whole body			**Metabolic and Nutritional**		
Asthenia	83 (16)	81 (16)	Peripheral Edema	51 (10)	41 (8)
Pain	70 (14)	73 (14)	**Musculoskeletal**		
Back Pain	60 (12)	68 (13)	Bone Pain	54 (11)	52 (10)
Headache	47 (9)	40 (8)	**Nervous**		
Abdominal Pain	40 (8)	38 (7)	Dizziness	30 (6)	22 (4)
Chest Pain	37 (7)	37 (7)	Insomnia	30 (6)	38 (7)
Flu Syndrome	35 (7)	30 (6)	Depression	23 (5)	32 (6)
Pelvic Pain	23 (5)	30 (6)	Hypertonia	16 (3)	26 (5)
Cardiovascular			**Respiratory**		
Vasodilation	128 (25)	106 (21)	Cough Increased	55 (11)	52 (10)
Hypertension	25 (5)	36 (7)	Dyspnea	51 (10)	47 (9)
Digestive			Pharyngitis	49 (10)	68 (13)
Nausea	94 (19)	106 (21)	**Skin and Appendages**		
Constipation	47 (9)	66 (13)	Rash	38 (8)	34 (8)
Diarrhea	40 (8)	33 (6)	**Urogenital**		
Vomiting	38 (8)	36 (7)	Leukorrhea	9 (2)	31 (6)
Anorexia	26 (5)	46 (9)			

[a] Patient may have had more than 1 adverse event.

Table 11

Adverse Event Group[a]	Number (N) and Percentage of Patients ARIMIDEX 1 mg (N=506)	NOLVADEX 20 mg (N=511)	Adverse Event Group[a]	Number (N) and Percentage of Patients ARIMIDEX 1 mg (N=506)	NOLVADEX 20 mg (N=511)
	N (%)	N (%)		N (%)	N (%)
Depression	23 (5)	32 (6)	Hot Flushes	134 (26)	118 (23)
Tumor Flare	15 (3)	18 (4)	Vaginal Dryness	9 (2)	3 (1)
Thromboembolic Disease[b]	18 (4)	33 (6)	Lethargy	6 (1)	15 (3)
Venous	5	15	Vaginal Bleeding	5 (1)	11 (2)
Coronary and Cerebral[c]	13	19	Weight Gain	11 (2)	8 (2)
Gastrointestinal Disturbance	170 (34)	196 (38)			

[a] Patient may have had more than 1 adverse event
[b] Includes pulmonary embolus, thrombophlebitis, retinal vein thrombosis
[c] Includes myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular accident, cerebral ischemia and cerebral infarct

Table 12

Adverse Event	Number (N) and Percentage of Patients with Adverse Event[†] ARIMIDEX 1 mg (N=262)	ARIMIDEX 10 mg (N=246)	Megestrol Acetate 160 mg (N=253)	Adverse Event	ARIMIDEX 1 mg (N=262)	ARIMIDEX 10 mg (N=246)	Megestrol Acetate 160 mg (N=253)
	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)
Asthenia	42 (16)	33 (13)	47 (19)	Pharyngitis	16 (6)	23 (9)	15 (6)
Pain	41 (16)	48 (20)	28 (11)	Dizziness	16 (6)	12 (5)	15 (6)
Headache	34 (13)	44 (18)	24 (9)	Rash	15 (6)	15 (6)	19 (8)
Back Pain	32 (12)	29 (11)	21 (8)	Dry Mouth	15 (6)	11 (4)	13 (5)
Chest Pain	28 (11)	38 (15)	29 (11)	Peripheral Edema	14 (5)	21 (9)	28 (11)
Abdominal Pain	28 (11)	26 (11)	19 (8)	Pelvic Pain	14 (5)	17 (7)	13 (5)
Nausea	24 (9)	27 (11)	53 (21)	Depression	14 (5)	6 (2)	5 (2)
Vomiting	24 (9)	26 (11)	16 (6)	Chest Pain	13 (5)	18 (7)	13 (5)
Cough Increased	22 (8)	18 (7)	19 (8)	Paresthesia	12 (5)	15 (6)	9 (4)
Diarrhea	22 (8)	18 (7)	7 (3)	Vaginal Hemorrhage	6 (2)	4 (2)	13 (5)
Constipation	18 (7)	18 (7)	21 (8)	Weight Gain	4 (2)	9 (4)	30 (12)
Abdominal Pain	18 (7)	14 (6)	18 (7)	Sweating	4 (2)	3 (1)	16 (6)
Anorexia	18 (7)	19 (8)	11 (4)	Increased Appetite	0 (0)	1 (0)	13 (5)
Dyspnea	17 (6)	26 (12)	19 (8)				

[†] Patient may have more than one adverse event.

Table 13

Adverse Event Group	Number (N) and Percentage of Patients ARIMIDEX 1 mg (N=262)	ARIMIDEX 10 mg (N=246)	Megestrol Acetate 160 mg (N=253)
	N (%)	N (%)	N (%)
Gastrointestinal Disturbance	77 (29)	81 (33)	54 (21)
Hot Flushes	33 (13)	29 (12)	35 (14)
Pain	19 (7)	28 (11)	35 (14)
Thromboembolic Disease	9 (3)	4 (2)	12 (5)
Vaginal Dryness	5 (2)	3 (1)	2 (1)
Weight Gain	4 (2)	10 (4)	30 (12)

ARIMIDEX may also be associated with rash including very rare cases of mucocutaneous disorders such as erythema multiforme and Stevens-Johnson syndrome. Very rare cases of allergic reactions including angioedema, urticaria and anaphylaxis have been reported in patients receiving ARIMIDEX.

OVERDOSAGE

Clinical trials have been conducted with ARIMIDEX, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of ARIMIDEX that results in life-threatening symptoms has not been established. In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m^2 basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage).

In an oral acute toxicity study in the dog the median lethal dose was greater than 45 mg/kg/day.

There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because ARIMIDEX is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

The dose of ARIMIDEX is one 1 mg tablet taken once a day. For patients with advanced breast cancer, ARIMIDEX should be continued until tumor progression.

For adjuvant treatment of early breast cancer in postmenopausal women, the optimal duration of therapy is unknown. In the ATAC trial ARIMIDEX was administered for five years.

Patients with Hepatic Impairment: (See **CLINICAL PHARMACOLOGY**) Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Although clearance of anastrozole was decreased in patients with cirrhosis due to alcohol abuse; plasma anastrozole concentrations stayed in the usual range seen in patients without liver disease. Therefore, no changes in dose are recommended for patients with mild-to-moderate hepatic impairment, although patients should be monitored for side effects. ARIMIDEX has not been studied in patients with severe hepatic impairment.

Patients with Renal Impairment: No changes in dose are necessary for patients with renal impairment.

Use in the Elderly: No dosage adjustment is necessary.

HOW SUPPLIED

White, biconvex, film-coated tablets containing 1 mg of anastrozole. The tablets are impressed on one side with a logo consisting of a letter "A" (upper case) with an arrowhead attached to the foot of the extended right leg of the "A" and on the reverse with the tablet strength marking "Adx 1". These tablets are supplied in bottles of 30 tablets (NDC 0310-0201-30).

Storage: Store at controlled room temperature, 20-25°C (68-77°F) [see USP].

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA
30261-02 Rev 05/07
253209

Shown in Product Identification Guide, page 306

CRESTOR® ℞

[krēs-tōr]
(rosuvastatin calcium)

DESCRIPTION

CRESTOR® (rosuvastatin calcium) is a synthetic lipid-lowering agent. Rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14. Its structural formula is:

[See structural formula at top of next column]

Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

CRESTOR Tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following inactive ingredi-

Continued on next page

...increase for AUC and C_{max} of rosuvastatin... ...is increase is considered to be clinically sig... ...RECAUTIONS, Drug Interactions, WARN... ...y/Rhabdomyolysis, DOSAGE AND ADMIN...

...administration of ezetimibe (10 mg) wit... ...0 mg) resulted in no significant changes i... ...rations of rosuvastatin or ezetimibe.

...ministration of an antacid (aluminum an... ...droxide combination) with rosuvastati... ...d in a decrease in plasma concentrations ... ...54%. However, when the antacid was give... ...osuvastatin, there were no clinically signi... ...a plasma concentrations of rosuvastatin (s... ...S, Information for Patients).

...tives: Coadministration of oral contrace... ...tradiol and norgestrel) with rosuvastatin i... ...rease in plasma concentrations of ethinyl e... ...gestrel by 26% and 34%, respectively.

...avir: Co-administration of CRESTOR an... ...product of two protease inhibitors (400 m... ...g ritonavir) in healthy volunteers was ass... ...approximately 2-fold and 5-fold increase i... ...eady-state $AUC_{(0-24)}$ and C_{max} respectivel... ...tween CRESTOR and other protease inhib... ...been examined. (See PRECAUTIONS, Dru...

...olemia (Heterozygous Familial and Nonh... ...ed Dyslipidemia (Fredrickson Type IIa an...

...uces total-C, LDL-C, ApoB, nonHDL-C, an... ...ses HDL-C, in patients with hypercholest... ...xed dyslipidemia. Therapeutic response i... ...week, and maximum response is usuall... ...n 4 weeks and maintained during long-ter...

...effective in a wide variety of adult patie... ...th hypercholesterolemia, with and witho... ...demia, regardless of race, gender, or age a... ...lations such as diabetics or patients with b... Experience in pediatric patients has be... ...nts with homozygous FH.

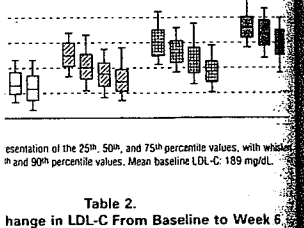
Study: In a multicenter, double-blin... ...led, dose-ranging study in patients with h... ...mia, CRESTOR given as a single daily do... ...significantly reduced total-C, LDL-C... ...d ApoB, across the dose range (Table 1).

Table 1.
...Response in Patients With Primary ...terolemia (Adjusted Mean % Change From... Baseline at Week 6)

...otal-C	LDL-C	Non HDL-C	ApoB	TG	HDL-C
-5	-7	-7	-3	-3	3
-33	-45	-44	-38	-35	13
-36	-52	-48	-42	-10	1
-40	-55	-51	-46	-23	8
-46	-63	-60	-54	-28	10

...led Study: CRESTOR was compared wi... ...reductase inhibitors atorvastatin, simv... ...avastatin in a multicenter, open-label, do... ...of 2,240 patients with Type IIa and IIb h... ...emia. After randomization, patients w... ...weeks with a single daily dose of eith... ...orvastatin, simvastatin, or pravastatin (F... ...le 2).

Figure 1.
...Change by Dose of CRESTOR, Atorvastatin, Simvastatin... ...n at Week 6 in Patients With Type IIa/IIb Dyslipidemia



...esentation of the 25th, 50th, and 75th percentile values, with whisker... ...th and 90th percentile values. Mean baseline LDL-C: 189 mg/dL.

Table 2.
...hange in LDL-C From Baseline to Week 6... by Treatment Group (sample sizes ranging... ...rom 156-167 patients per group)

Treatment Daily Dose 10 mg	20 mg	40 mg	80 mg
-46*	-52†	-55†	-5...
-37	-43	-48	-5...
-20	-24	-30	-3...
-28	-35	-39	-4...

10 mg reduced LDL-C significantly mo... ...astatin 10 mg; pravastatin 10 mg, 20 mg, a... ...vastatin 10 mg, 20 mg, and 40 mg. (p<0.00...

...CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)

...CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg and 80 mg. (p<0.002)

...Corresponding standard errors are approximately 1.00

...Heterozygous Familial Hypercholesterolemia

...In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (Table 3).

Table 3.
Mean LDL-C Percentage Change from Baseline

		CRESTOR (n=435) LS Mean[e] (95% CI)	Atorvastatin (n=187) LS Mean (95% CI)
Week 6	20 mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40 mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80 mg	NA	-52% (-54%, -50%)

[e] LS Means are least square means adjusted for baseline LDL.

...Hypertriglyceridemia
...(Fredrickson Type IIb & IV)

...In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 4).

...[See table 4 above]

...Homozygous Familial Hypercholesterolemia

...In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

INDICATIONS AND USAGE

CRESTOR is indicated:

- as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
- as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
- to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

According to NCEP-ATPIII guidelines, therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for coronary heart disease due to hypercholesterolemia. The two major modalities of LDL-lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. The TLC Diet stresses reductions in saturated fat and cholesterol intake. Table 5 defines LDL-C goals and cutpoints for initiation of TLC and for drug consideration.

[See table 5 above]

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, nonHDL-C (total-C minus HDL-C) becomes a secondary target of therapy. NonHDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for a coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥ 130 mg/dL (see NCEP Treatment Guidelines, above).

Patients >20 years of age should be screened for elevated cholesterol levels every 5 years.

Prior to initiating therapy with CRESTOR, secondary causes for hypercholesterolemia (e.g., poorly-controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias.

CONTRAINDICATIONS

CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product.

Table 4.
Dose-Response in Patients With Primary Hypertriglyceridemia Over 6 Weeks
Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo N=26	CRESTOR 5 mg N=25	CRESTOR 10 mg N=23	CRESTOR 20 mg N=27	CRESTOR 40 mg N=25
Triglycerides	1 (-40, 72)	-21 (-58, 38)	-37 (-65, 5)	-37 (-72, 11)	-43 (-80, -7)
NonHDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, 12)	-51 (-62, -6)
VLDL-C	2 (-36, 53)	-25 (-62, 49)	-48 (-72, 14)	-49 (-83, 20)	-56 (-83, 10)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

Table 5.
NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL level at which to initiate TLC	LDL level at which to consider drug therapy
CHD[a] or CHD Risk Equivalent (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)[b]
2+ Risk Factors (10-year risk ≤ 20%)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL 10-year risk 10-20%
			≥160 mg/dL 10-year risk <10%
0-1 Risk Factor[c]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL (LDL-lowering drug optional)

[a] CHD = coronary heart disease.
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C <100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes).

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS).

Myopathy/Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency.

Consequently:

1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and inadequately treated hypothyroidism.
2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.
3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION).
4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions).**
5. **The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General).**
6. **Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).**

PRECAUTIONS

General

Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appro-

Continued on next page

ed Fixed Dose Study in

MIRAPEX 0.75 mg (N = 90) %	Placebo (n = 86) %
27	5
7	0
4	7
7	1
7	5
13	9
8	2
6	1
7	1

y 2-fold greater than placebo for ater than 3 mg/day. The incidence of ith pramipexole at a dose of 1.5 mg/ placebo.

lets are used in combination with f the levodopa dosage should be con- study in advanced Parkinson's dis- odopa was reduced by an average of

h Renal Impairment

osage in Parkinson's Disease pairment

	Starting Dose (mg)	Maximum Dose (mg)
ment /min)	0.125 TID	1.5 TID
9 mL/	0.125 BID	1.5 BID
4 mL/	0.125 QD	1.5 QD
t /min nts)	The use of MIRAPEX tablets has not been adequately studied in this group of patients.	

tment

MIRAPEX tablets be discontinued : in some studies, however, abrupt eventful.

e

ting dose of MIRAPEX tablets is ily 2–3 hours before bedtime. For ional symptomatic relief, the dose 4–7 days (Table 9). Although the s was increased to 0.75 mg in some n open-label treatment, there is no ng dose provides additional benefit

age Schedule of MIRAPEX tablets for RLS

on	Dosage (mg) to be taken once daily, 2–3 hours before bedtime
ys	0.125
ys	0.25
ys	0.5

Patients with Renal Impairment

The duration between titration steps should be increased to 2 days in RLS patients with severe and moderate renal impairment (creatinine clearance 20-60 mL/min) (see CLINICAL PHARMACOLOGY, *Renal Insufficiency*).

Discontinuation of Treatment

In clinical trials of patients being treated for RLS with doses up to 0.75 mg once daily, Mirapex® (pramipexole dihydrochloride) tablets were discontinued without a taper.

HOW SUPPLIED

MIRAPEX tablets are available as follows:

0.125 mg: white, round tablet with "BI" on one side and "85" on the reverse side.
Bottles of 90 NDC 0597-0183-90

0.25 mg: white, oval, scored tablet with "BI BI" on one side and "84 84" on the reverse side.
Bottles of 90 NDC 0597-0184-90
Unit dose packages of 100 NDC 0597-0184-61

0.5 mg: white, oval, scored tablet with "BI BI" on one side and "85 85" on the reverse side.
Bottles of 90 NDC 0597-0185-90
Unit dose packages of 100 NDC 0597-0185-61

1 mg: white, round, scored tablet with "BI BI " on one side and "90 90" on the reverse side.
Bottles of 90 NDC 0597-0190-90
Unit dose packages of 100 NDC 0597-0190-61

1.5 mg: white, round, scored tablet with "BI BI" on one side and "91 91" on the reverse side.
Bottles of 90 NDC 0597-0191-90
Unit dose packages of 100 NDC 0597-0191-61

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature]. Protect from light.

Store in a safe place out of the reach of children.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg TID). In a similar study of pigmented rats with 2 years exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on a mg/m^2 basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2 and 11 times the highest clinical dose on a mg/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m^2 basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

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U.S. Patent Nos. 4,886,812; 6,001,861; and 6,194,445.

Revised: November 7, 2006
OT1317D
10003128/US/3 10003129/US/3
2001/01

MIRAPEX®
(pramipexole dihydrochloride)
0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg Tablets

Patient Information

Mirapex® *[mir'-ah-pĕx]* (pramipexole dihydrochloride) tablets

Read the Patient Information that comes with MIRAPEX before you start taking it and each time you get a refill. There may be some new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about MIRAPEX?

MIRAPEX may cause you to fall asleep while you are doing daily activities such as driving, talking with other people, watching TV, or eating.

- Some people taking MIRAPEX have had car accidents because they fell asleep while driving.
- Some patients did not feel sleepy before they fell asleep while driving. You could fall asleep without any warning.

Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how MIRAPEX affects you.

Tell your doctor right away if you fall asleep while you are doing activities such as talking with people, watching TV, eating, or driving, or if you feel sleepier than is normal for you.

What is MIRAPEX?

MIRAPEX is a prescription medicine to treat

- primary Restless Legs Syndrome.
- signs and symptoms of Parkinson's disease.

MIRAPEX has not been studied in children.

Who should not take MIRAPEX?

Do not take MIRAPEX if you are allergic to pramipexole or any of the inactive ingredients of MIRAPEX. See the end of this leaflet for a complete list of ingredients in MIRAPEX.

What should I tell my doctor before taking MIRAPEX?

Tell your doctor about all of your medical conditions, including if you

- feel sleepy during the day from a sleep problem other than Restless Legs Syndrome.
- have low blood pressure, or if you feel dizzy or faint, especially when getting up from a lying or sitting position.
- have trouble controlling your muscles (dyskinesia).
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if MIRAPEX will harm your unborn baby.
- are breast feeding. It is not known if MIRAPEX will pass into your breast milk. You and your doctor should decide if you will take MIRAPEX or breastfeed. You should not do both.
- drink alcohol. Alcohol can increase the chance that MIRAPEX will make you feel sleepy or fall asleep when you should be awake.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take any other medicines that make you sleepy. MIRAPEX and other medicines may interact with each other causing side effects. MIRAPEX may affect the way other medicines work, and other medicines may affect how MIRAPEX works.

How should I take MIRAPEX?

- Take MIRAPEX exactly as your doctor tells you to. Your doctor will tell you how many MIRAPEX tablets to take and when to take them.
- Your doctor may change your dose until you are taking the right amount of medicine to control your symptoms. Do not take more or less MIRAPEX than your doctor tells you to.
- MIRAPEX can be taken with or without food. Taking MIRAPEX with food may lower your chances of getting nausea.
- If you miss a dose, **do not double your next dose.** Skip the dose you missed and take your next regular dose.
- Be sure to tell your doctor right away if you stop taking MIRAPEX for any reason. Do not start taking MIRAPEX again before speaking with your doctor. If you have Parkinson's disease and are stopping Mirapex, you should stop Mirapex slowly over 7 days.

What should I avoid while taking MIRAPEX?

- **Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how MIRAPEX affects you.** See **"What is the most important information I should know about MIRAPEX?"** at the beginning of this leaflet.
- Do not drink alcohol while taking MIRAPEX. It can increase your chances of feeling sleepy or falling asleep when you should be awake.

What are the possible side effects of MIRAPEX?

MIRAPEX can cause serious side effects, including

- **falling asleep during normal daily activities.** See **"What is the most important information I should know about MIRAPEX?"**
- **low blood pressure when you sit or stand up quickly.** You may have dizziness, nausea, fainting, or sweating. Sit and stand up slowly after you have been sitting or lying down for a while.
- **hallucinations.** You may see, hear, feel, or taste something that isn't there. You have a higher chance of having hallucinations if you are over 65 years old.

The most common side effects in people taking MIRAPEX for Restless Legs Syndrome are nausea and sleepiness.

The most common side effects in people taking MIRAPEX for Parkinson's disease are nausea, dizziness, sleepiness, constipation, hallucinations, insomnia, muscle weakness, confusion, and abnormal movements.

These are not all the possible side effects of MIRAPEX. For more information ask your doctor or pharmacist.

Be sure to talk to your doctor about any side effects that bother you or that do not go away.

Other Information about Mirapex

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the medicines used to treat Parkinson's disease. Mirapex is one of the medicines used to treat Parkinson's disease, therefore, patients being treated with Mirapex should have periodic skin examinations.

There have been reports of patients taking certain medicines to treat Parkinson's disease or RLS, including MIRAPEX, that have reported problems with gambling, compulsive eating, and increased sex drive. It is not possible to reliably estimate how often these behaviors occur or to determine which factors may contribute to them. If you or your family members notice that you are developing unusual behaviors, talk to your doctor.

How should I store MIRAPEX?

- Store MIRAPEX at room temperature at 59°F to 86°F (15°C to 30°C).
- Keep MIRAPEX out of light.
- **Keep MIRAPEX and all medicines out of the reach of children.**

General information about MIRAPEX

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. Do not take MIRAPEX for a condition for which it was not prescribed. Do not share MIRAPEX with other people, even if they have the same symptoms you do. It may harm them.

This Patient Information leaflet summarizes the most important information about MIRAPEX. For more information, talk with your doctor or pharmacist. They can give you information about MIRAPEX that is written for healthcare professionals. **For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.**

What are the ingredients in MIRAPEX?

Active Ingredient: pramipexole dihydrochloride monohydrate

Inactive Ingredients: mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate

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2001/01

Shown in Product Identification Guide, page 308

"ATTENTION DISPENSER: Accompanying Medication Guide must be dispensed with this product."

℞

MOBIC®
[mō-bĭc]
(meloxicam)
Tablets 7.5 mg and 15 mg
and
MOBIC®
(meloxicam)
Oral Suspension 7.5 mg/5 mL
Rx only

Prescribing Information

WARNING

Cardiovascular Risk

- **NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS and CLINICAL TRIALS).**
- **MOBIC tablets/oral suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).**

Gastrointestinal Risk

- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any**

Continued on next page

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he treatment of the signs and symp
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n patients 2 years of age and older
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Both studies included three arms:
es of meloxicam. In both studies,

meloxicam dosing began at 0.125 mg/kg/day (7.5 mg maximum) or 0.25 mg/kg/day (15 mg maximum), and naproxen dosing began at 10 mg/kg/day. One study used these doses throughout the 12-week dosing period, while the other incorporated a titration after 4 weeks to doses of 0.25 mg/kg/day and 0.375 mg/kg/day (22.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen.

The efficacy analysis used the ACR Pediatric 30 responder definition, a composite of parent and investigator assessments, counts of active joints and joints with limited range of motion, and erythrocyte sedimentation rate. The proportion of responders were similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of Mobic® (meloxicam) tablets/oral suspension and other treatment options before deciding to use MOBIC tablets/oral suspension. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

MOBIC tablets/oral suspension is indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

MOBIC tablets/oral suspension is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older.

CONTRAINDICATIONS

MOBIC tablets/oral suspension is contraindicated in patients with known hypersensitivity to meloxicam.

MOBIC tablets/oral suspension should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS, Anaphylactoid Reactions,** and **PRECAUTIONS, Pre-existing Asthma**).

MOBIC tablets/oral suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **WARNINGS, Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension

NSAIDs, including Mobic® (meloxicam) tablets/oral suspension, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including MOBIC tablets/oral suspension, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. MOBIC tablets/oral suspension should be used with caution in patients with fluid retention, hypertension, or heart failure.

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including MOBIC tablets/oral suspension, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs, occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs, including Mobic® (meloxicam) tablets/oral suspension, can result in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors, and angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of MOBIC tablets/oral suspension in patients with advanced renal disease. Therefore, treatment with MOBIC tablets/oral suspension is not recommended in these patients with advanced renal disease. If MOBIC tablets/oral suspension therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDS, anaphylactoid reactions have occurred in patients without known prior exposure to MOBIC tablets/oral suspension. MOBIC tablets/oral suspension should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS, Pre-existing Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including MOBIC tablets/oral suspension, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, MOBIC tablets/oral suspension should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

Mobic® (meloxicam) tablets/oral suspension cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of MOBIC tablets/oral suspension in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including MOBIC tablets/oral suspension. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MOBIC tablets/oral suspension. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), MOBIC tablets/oral suspension should be discontinued.

Renal Effects

Caution should be used when initiating treatment with MOBIC tablets/oral suspension in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with MOBIC tablets/oral suspension. Caution is also recommended in patients with pre-existing kidney disease (see **WARNINGS, Renal Effects** and **Advanced Renal Disease**).

The extent to which metabolites may accumulate in patients with renal failure has not been studied with MOBIC tablets/oral suspension. Because some MOBIC tablets/oral suspension metabolites are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including MOBIC tablets/oral suspension. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including MOBIC tablets/oral suspension, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

Drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving Mobic® (meloxicam) tablets/oral suspension who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, MOBIC tablets/oral suspension should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. MOBIC tablets/oral suspension, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).
2. MOBIC tablets/oral suspension, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation**).
3. MOBIC tablets/oral suspension, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).

Continued on next page

Spiriva—Cont.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos. RE38,912, 5,610,163, 6,777,423, 6,903,928, and 7,070,800 with other patents pending. The HandiHaler® inhalation device is covered by U.S. Design Patent No. D355,029 with other patents pending.

IT1600I 10004551/US1 65626/US/1

Revised: October 24, 2006
SP282222 SV39202
Shown in Product Identification Guide, page 308

VIRAMUNE® ℞
[vī-r-ă-mewn]
(nevirapine) Tablets
VIRAMUNE® ℞
(nevirapine) Oral Suspension
Rx only

WARNING

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with VIRAMUNE®. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4 counts at initiation of therapy place patients at increased risk; women with CD4 counts >250 cells/mm^3, including pregnant women receiving VIRAMUNE in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all CD4 counts and at any time during treatment. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue VIRAMUNE and seek medical evaluation immediately (see WARNINGS).

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately (see WARNINGS).

It is essential that patients be monitored intensively during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart VIRAMUNE following severe hepatic, skin or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed (see WARNINGS).

DESCRIPTION

VIRAMUNE is the brand name for nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds.

VIRAMUNE Tablets are for oral administration. Each tablet contains 200 mg of nevirapine and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate.

VIRAMUNE Oral Suspension is for oral administration. Each 5 mL of VIRAMUNE suspension contains 50 mg of nevirapine (as nevirapine hemihydrate). The suspension also contains the following excipients: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide and purified water.

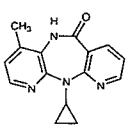
The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',3'-e][1,4] diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.30 and the molecular formula $C_{15}H_{14}N_4O$. Nevirapine has the following structural formula:

[See structural formula at top of next column]

MICROBIOLOGY

Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse



transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Antiviral Activity

The antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. In recent studies using human cord blood lymphocytes and human embryonic kidney 293 cells, EC50 values (50% inhibitory concentration) ranged from 14-302 nM against laboratory and clinical isolates of HIV-1. Nevirapine exhibited antiviral activity in cell culture against group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF) CRF01_AE, CRF02_AG and CRF12_BF (median EC50 value of 63 nM). Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates. Nevirapine in combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

Resistance

HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance in cell culture was not altered when selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II trials over 1 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations. Nineteen of these patients (80%) had isolates with Y181C mutations regardless of dose.

Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

Cross-resistance

Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in cell culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs delavirdine and efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTI's ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

ANIMAL PHARMACOLOGY

Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

Absorption and Bioavailability: Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 μg/mL (7.5 μM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 μg/mL (17 ± 7 μM), (n = 242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When VIRAMUNE (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure (AUCτ) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. VIRAMUNE may be administered with or without food, antacid or didanosine.

Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk (see **PRECAUTIONS, *Nursing Mothers***). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1–10 μg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A4 and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ^{14}C-nevirapine, approximately 91.4 ±10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound. Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6. Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A4 and CYP2B6 mediated metabolism leads to an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Pharmacokinetics in Special Populations

Renal Impairment: HIV seronegative adults with mild (CrCL 50-79 mL/min; n=7), moderate (CrCL 30-49 mL/min; n=6), or severe (CrCL <30 mL/min; n=4) renal impairment received a single 200 mg dose of nevirapine in a pharmacokinetic study. These subjects did not require dialysis. The study included six additional subjects with renal failure requiring dialysis.

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. However, subjects requiring dialysis exhibited a 44% reduction in nevirapine AUC over a one-week exposure period. There was also evidence of accumulation of nevirapine hydroxy-metabolites in plasma in subjects requiring dialysis. An additional 200 mg dose following each dialysis treatment is indicated (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

Hepatic Impairment: HIV seronegative adults with mild (Child-Pugh Class A; n=6) or moderate (Child-Pugh Class B; n=4) hepatic impairment received a single 200 mg dose of nevirapine in a pharmacokinetic study.

In the majority of patients with mild or moderate hepatic impairment, no significant changes were seen in the pharmacokinetics of nevirapine. However, a significant increase in the AUC of nevirapine observed in one patient with Child-Pugh Class B and ascites suggests that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, a single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see **PRECAUTIONS**). Nevirapine should not be administered to patients with severe hepatic impairment (see **WARNINGS**).

Gender: In the multinational 2NN study, a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8% lower clearance of nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

Race: An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 μg/mL Black, 3.8 μg/mL Hispanic, 4.3 μg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Geriatric Patients: Nevirapine pharmacokinetics in HIV-1-infected adults do not appear to change with age (range 18–68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.

Pediatric Patients: The pharmacokinetics of nevirapine have been studied in two open-label studies in children with

HIV-1 infection. In one s
HIV-1-infected children ra
years were administered
120 mg per m^2; n=3 per do
an overnight fast. The mea
adjusted for body weight w
to adults.

In a multiple dose study
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tered as monotherapy or
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following demographics: m
(73%), median age of 11 mo
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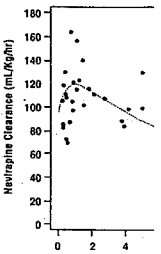
nevirapine for approximat
m^2/BID (patients > 9 year
tients ≤ 9 years of age). Ne
justed for body weight reac
2 years and then decreased
apparent clearance adjust
two-fold greater in children
to adults. The relationshi
with long term drug admi
Figure 1. The pediatric dosi
der to achieve steady-state
atric patients that approxi
AGE AND ADMINISTRA

Figure 1: Nevirapine Apparent Cle



Drug Interactions: (see P
tions) Nevirapine induces
bolic isoenzymes 3A4 a
VIRAMUNE and drugs pri
or CYP2B6 may result in d
of these drugs and attenua
While primarily an induce
2B6 enzymes, nevirapine
Among human hepatic cyt
capable *in vitro* of inhibiti
warfarin (CYP3A4). The es
CYP3A4 was 270 μM, a con
achieved in patients as th
Therefore, nevirapine may
on other substrates of CYP
Nevirapine does not appea
tions of drugs that are subs
systems, such as 1A2, 2D6,
Table 1 (see below) contain
studies performed with VIR
to be co-administered. The
AUC, C_{max}, and C_{min} of co-
rized. To measure the full
action effect following indu
tant drug at steady state
VIRAMUNE (200 mg QD
BID for 14 days) followed b
the concomitant drug.
[See table 1 above]
Because of the design of the
of 28 days of VIRAMUNE t
the effect of the concomita
steady state concentrations
historical controls.
Administration of rifampin
on nevirapine pharmacokin
by greater than 50%. Admin
in an approximate 100% ir
based on a comparison to
TIONS, *Drug Interactions*
drugs listed in Table 1 on n
not significant.

INDICATIONS AND USA

VIRAMUNE (nevirapine) is
tion with other antiretrovi
HIV-1 infection. This indic
clinical trial (BI 1090) tha
pression of HIV-RNA and t
one of which (BI 1046) is de
Additional important info
VIRAMUNE for the treatm
- Based on serious and l
observed in controlled
VIRAMUNE should not b
CD4+ cell counts greater
males with CD4+ cell cou
unless the benefit outwei

d if you are taking ATRIPLA. The Ce
ontrol and Prevention recommend th
not breast-feed because they can pa
their milk to the baby. Also, ATRIPL
breast milk and cause serious harm
th your healthcare provider if you ar
ou should stop breast-feeding or, ma
rent medicine.
with alcohol or other medicines causin
as ATRIPLA, such as drowsiness, m
effects.
ther medicines, including prescriptio
n medicines and herbal products, wit
your healthcare provider.
s that can spread HIV infection sinc
stop you from passing the HIV infe

le side effects of ATRIPLA?
the following serious side effects:
ldup of an acid in the blood). Lactic a
dical emergency and may need to b
tal. Call your healthcare provider righ
ns of lactic acidosis. (See "What is th
information I should know about

ems, with liver enlargement (hepato
the liver (steatosis). Call your health
away if you get any signs of liver prob
is the most important information
ATRIPLA?")
atitis B Virus (HBV) infection, in whic
y returns in a worse way than before
e HBV and you stop taking ATRIPLA
vider will monitor your condition for
r stopping ATRIPLA if you have both
ction and may recommend treatment

problems. A small number of patients
ere depression, strange thoughts, or
ile taking ATRIPLA. Some patients
cide and a few have actually commit
roblems may occur more often in pa
mental illness. Contact your health
way if you think you are having these
s, so your healthcare provider can de
ntinue to take ATRIPLA.
you have had kidney problems in the
edicines that can cause kidney prob
re provider should do regular blood
idneys.
neral density (thinning bones). It is
ong-term use of ATRIPLA will cause
s. If you have had bone problems in
care provider may need to do tests fo
eral density or may prescribe medi
ne mineral density.

ziness, headache, trouble sleeping,
ncentrating, and/or unusual dreams
ATRIPLA. These side effects may be
TRIPLA at bedtime on an empty stom
go away after you have taken the
ks. If you have these common side
s, it does not mean that you will also
c problems, such as severe depres
or angry behavior. Tell your health
if any of these side effects continue
s possible that these symptoms may
PLA is used with alcohol or mood al

ouble concentrating, or are drowsy,
y be dangerous, such as driving or

lashes usually go away without any
a small number of patients, rash
evelop a rash, call your healthcare

ts include tiredness, upset stomach,
hea.
cts with ATRIPLA include:
hanges in body fat develop in some
IIV medicine. These changes may
mount of fat in the upper back and
, in the breasts, and around the
the legs, arms, and face may also
d long-term health effects of these
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all spots or freckles) may also hap

vider or pharmacist if you notice
ing ATRIPLA.
provider before stopping ATRIPLA
for any other reason.
list of side effects possible with
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le effects of ATRIPLA and all the

other medicines out of reach of

temperature 77° F (25° C).
iginal container and keep the con

hat is out of date or that you no
w any medicines away make sure
nd them.

General information about ATRIPLA:
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ATRIPLA for a condition for which it was not prescribed. Do not give ATRIPLA to other people, even if they have the same symptoms you have. It may harm them.
This leaflet summarizes the most important information about ATRIPLA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ATRIPLA that is written for health professionals.
Do not use ATRIPLA if the seal over bottle opening is broken or missing.
What are the ingredients of ATRIPLA?
Active ingredients: efavirenz, emtricitabine, and tenofovir disoproxil fumarate
Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, microcrystalline cellulose, magnesium stearate, sodium lauryl sulfate. The film coating contains black iron oxide, polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, and titanium dioxide.
Rx Only
May 2007
GS-21-937-003
ATRIPLA™ is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. EMTRIVA, TRUVADA, and VIREAD are trademarks of Gilead Sciences, Inc. SUSTIVA is a trademark of Bristol-Myers Squibb Pharma Company. Reyataz and Videx are trademarks of Bristol-Myers Squibb Company. Pravachol is a trademark of ER Squibb & Sons, LLC. Other brands listed are the trademarks of their respective owners.

J.R. Carlson Laboratories, Inc.

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ARLINGTON HEIGHTS, IL 60004-1985

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In Emergencies:
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FAX: (847) 255-1605

CARLSON NORWEGIAN COD LIVER OIL OTC

Each Teaspoonful of Carlson Norwegian Cod Liver Oil provides:

		% DV
Total Omega 3 Fatty Acids	1100 mg to 1250 mg**	*
DHA (Docosahexaenoic Acid)	500 mg to 590 mg**	*
EPA (Eicosapentaenoic Acid)	360 mg to 500 mg**	*
ALA (Alpha-linolenic Acid)	40 mg to 60 mg**	*
Vitamin A	700 IU to 1,200 IU**	14% to 24%
Vitamin D	400 IU	100%
Vitamin E	10 IU	33%
Norwegian Cod Liver Oil	4.6 g	*

** Naturally Occurring Variations.

DESCRIPTION
Carlson Norwegian Cod Liver oil comes from the livers of fresh cod fish found in the arctic coastal waters of Norway.
Suggested Use: Take one teaspoonful daily at mealtime.
This product is regularly tested (using AOAC international protocols) for freshness, potency, and purity by an independent, FDA-registered laboratory and has been determined to be fresh, fully-potent and free of detectable levels of mercury, cadmium, lead, PCB's and 28 other contaminants.

HOW SUPPLIED
Supplied in bottles of 250ml and 500ml. Lemon or regular flavor.

E-GEMS® OTC

DESCRIPTION
100% natural-source vitamin E (d-alpha tocopheryl acetate) soft gels. Available in 8 strengths: 30 IU, 100 IU, 200 IU, 400 IU, 600 IU, 800 IU, 1000 IU, 1200 IU.

HOW SUPPLIED
Supplied in a variety of bottle sizes.

MED OMEGA™ FISH OIL 2800 OTC

(mĕd ōmĕga)
Balanced Concentrate
DHA 1200 mg & EPA 1200 mg
Professional Strength Dietary Supplement

DESCRIPTION
From Norway: The finest fish oil from deep, cold ocean-water fish. Concentrated to supply 2800 mg (2.8 grams) of total omega 3's per teaspoonful. Bottled in Norway to ensure maximum freshness. Refreshing natural orange taste.

Supplement Facts

Serving Size 1 Teaspoonful (5 ml)	Servings Per Container 20	
Each Teaspoonful Contains		% D.V.
Omega-3 Fatty Acids	2.8 g (2800 mg)	*
EPA (eicosapentaenoic acid)	1.2 g (1200 mg)	*
DHA (docosehexaenoic acid)	1.2 g (1200 mg)	*
Other Omega-3 Fatty acids	.4 g (400 mg)	*
Vitamin E (d-Alpha Tocopherol)	10 IU	33%

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value (D.V.) not established.

This product is regularly tested (using AOAC international protocols) for freshness, potency and purity by an independent, FDA-registered laboratory and has been determined to be fresh, fully-potent and free of detectable levels of mercury, cadmium, lead, PCB's and 28 other contaminants.

Other Ingredients: Natural orange flavor, rosemary extract, ascorbyl palmitate, natural tocopherols.

DIRECTIONS
Take one teaspoonful daily AT MEALTIME.
Try it on popcorn & salads.
REFRIGERATE: To retain freshness after initially opening the bottle, keep refrigerated and preferably use within 2 months.

* This Statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease.

ORANGE FLAVOR
100 ML. (3.35 FL. OZ.)
Manufactured & bottled in Norway for
J.R. Carlson Laboratories, Inc., Arlington Hts., IL 60004-1985
888-234-5656 • 847-255-1600 • www.carlsonlabs.com

SUPER OMEGA-3 OTC

DESCRIPTION
Carlson Super Omega-3 soft gels contain a special concentrate of fish body oils from deep cold-water fish, which are rich in EPA & DHA.
Each soft gelatin capsule provides 1000 mg of omega-3 fish oils consisting of:

		% U.S. RDA
EPA (eicosapentaenoic acid)	300 mg	*
DHA (docosahexaenoic acid)	200 mg	*
Other Omega-3's	100 mg	*
Vitamin E (d-alpha tocopherol)	10 IU	33%

This product is regularly tested (using AOAC international protocols) for freshness, potency and purity by an independent, FDA-registered laboratory and has been determined to be fresh, fully-potent and free of detectable levels of mercury, cadmium, lead, PCB's and 28 other contaminants.

HOW SUPPLIED
In bottles of 50, 100, 250.

Celltech Pharmaceuticals, Inc.

for product information, please see UCB Inc.

Centocor, Inc.

200 GREAT VALLEY PARKWAY
MALVERN, PA 19355
USA

Direct General Inquiries to:
Ph: (610) 651-6000
Fax: (610) 651-6100
Medical Emergency Contact:
Ph: (800) 457-6399
For Medical Information/Adverse Experience Reporting Contact:
Medical Information
Ph: (800) 457-6399

REMICADE® ℞

(infliximab)
for IV Injection

WARNINGS

RISK OF INFECTIONS
Patients treated with REMICADE are at increased risk for infections, including progression to serious infections leading to hospitalization or death (see WARNINGS and ADVERSE REACTIONS). These infections have included bacterial sepsis, tuberculosis, invasive fungal and other opportunistic infections. Patients should be educated about the symptoms of infection, closely monitored for signs and symptoms of infection during and after treatment with REMICADE, and should have access to appropriate medical care. Patients who develop an infection should be evaluated for appropriate antimicrobial therapy and for serious infections REMICADE should be discontinued.
Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving REMICADE. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection[1,2] prior to initiating REMICADE and during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with REMICADE. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving REMICADE. Some patients who tested negative for latent tuberculosis prior to receiving REMICADE have developed active tuberculosis. Physicians should monitor patients receiving REMICADE for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

HEPATOSPLENIC T-CELL LYMPHOMAS
Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with REMICADE have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.

DESCRIPTION
REMICADE is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.
REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

CLINICAL PHARMACOLOGY

General
Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[3,4] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, ac-

Continued on next page

Remicade—Cont.

thereafter through week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to week 46 at the investigator's discretion.

Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both REMICADE groups achieved clinical response, clinical remission and mucosal healing than in the placebo group. Each of these effects was maintained through the end of each trial (week 54 in Study UC I, and week 30 in Study UC II). In addition, a greater proportion of patients in REMICADE groups demonstrated sustained response and sustained remission than in the placebo groups (Table 9).

Of patients on corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups were in clinical remission and able to discontinue corticosteroids at week 30 compared with the patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through week 54 (21% in REMICADE treatment groups vs. 9% in placebo group). The REMICADE-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

[See table 9 at bottom of previous page]

The improvement with REMICADE was consistent across all Mayo subscores through week 54 (Study UC I shown in Table 10; Study UC II through week 30 was similar).

Table 10
PROPORTION OF PATIENTS IN STUDY UC I WITH MAYO SUBSCORES INDICATING INACTIVE OR MILD DISEASE THROUGH WEEK 54

	Study UC I		
		REMICADE	
	Placebo (n=121)	5 mg/kg (n=121)	10 mg/kg (n=122)
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Week 54	31%	52%	51%
Rectal bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Week 54	62%	69%	67%
Physician's global assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
Week 54	26%	53%	53%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%
Week 54	21%	50%	51%

INDICATIONS AND USAGE

Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (see Boxed WARNINGS, WARNINGS, and PRECAUTIONS-Pediatric Use).

REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

Ankylosing Spondylitis

REMICADE is indicated for reducing signs and symptoms

Plaque Psoriasis

REMICADE is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. REMICADE should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician (see Boxed WARNINGS, WARNINGS, and PRECAUTIONS).

Ulcerative Colitis

REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

CONTRAINDICATIONS

REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with Heart Failure).

REMICADE should not be re-administered to patients who have experienced a severe hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

WARNINGS

RISK OF INFECTIONS

(See Boxed WARNINGS)

Serious infections, including sepsis and pneumonia, have been reported in patients receiving TNF-blocking agents. Some of these infections have been fatal. Although some of the serious infections in patients treated with REMICADE have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infections, some patients who were hospitalized or had a fatal outcome from infection were treated with REMICADE alone.

REMICADE should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of REMICADE in patients with a chronic infection or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection while on or after treatment with REMICADE. New infections should be closely monitored. If a patient develops a serious infection, REMICADE therapy should be discontinued (see ADVERSE REACTIONS: Infections).

Cases of tuberculosis, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, other bacterial, mycobacterial and fungal infections have been observed in patients receiving REMICADE. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with REMICADE. When tuberculin skin testing is performed for latent tuberculosis infection an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG).

Patients receiving REMICADE should be monitored closely for signs and symptoms of active tuberculosis, particularly since tests for latent tuberculosis infection may be falsely negative. The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with REMICADE should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with REMICADE. Anti-tuberculosis therapy should be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating REMICADE should also be considered in patients who have several or highly significant risk factors for tuberculosis infection[14] and have a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of REMICADE treatment should be carefully considered before initiation of REMICADE therapy.

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra

Rare post-marketing cases of hepatosplenic T-cell lymphomas have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE. All these reports have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. The clinical course of this disease is very aggressive with a fatal outcome in most patients within 2 years of diagnosis. The causal relationship of hepatosplenic T-cell lymphoma to REMICADE therapy remains unclear.

Hepatitis B Virus Reactivation

Use of TNF blockers, including REMICADE has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers, including REMICADE, for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in post-marketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., 5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild to moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity).

Patients with Heart Failure

REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure (see CONTRAINDICATIONS and ADVERSE REACTIONS, Patients with Heart Failure).

Hematologic Events

Cases of leukopenia, neutropenia, thrombocytopenia and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms of dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities.

Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, occurred during or within 2 hours of REMICADE

Trisenox—Cont.

REFERENCES

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Rx only

Manufactured for:
Cephalon®
Cephalon, Inc.
Frazer, PA 19355
Revised February 2006
U.S. Patent Nos. 6,723,351; 6,855,339; 6,861,076; 6,884,439
 101874/3

Shown in Product Identification Guide, page 309

VIVITROL®

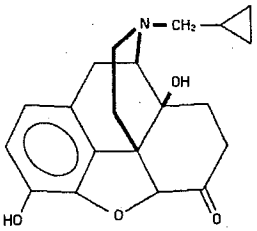
℞

[vī-vī-trōl]
380 mg/vial
(naltrexone for extended-release injectable suspension)

DESCRIPTION:

VIVITROL® (naltrexone for extended-release injectable suspension) is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. Naltrexone is an opioid antagonist with little, if any, opioid agonist activity.

Naltrexone is designated chemically as morphinan-6-one, 17 - (cyclopropylmethyl) - 4,5 - epoxy - 3,14 - dihydroxy-(5α) (CAS Registry # 16590-41-3). The molecular formula is $C_{20}H_{23}NO_4$ and its molecular weight is 341.41 in the anhydrous form (i.e., < 1% maximum water content). The structural formula is:



Naltrexone base anhydrous is an off-white to a light tan powder with a melting point of 168-170° C (334-338°F). It is insoluble in water and is soluble in ethanol.

VIVITROL is provided as a carton containing a vial each of VIVITROL microspheres and diluent, one 5-mL syringe, one ½-inch 20-gauge preparation needle, and two 1½-inch 20-gauge administration needles with safety device.

VIVITROL microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380-mg naltrexone per vial. Naltrexone is incorporated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres.

The diluent is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres must be suspended in the diluent prior to injection.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Mechanism of Action

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of VIVITROL is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, VIVITROL will precipitate withdrawal symptomatology.

Occupation of opioid receptors by naltrexone may block the effects of endogenous opioid peptides. The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. However, involvement of the endogenous opioid system is suggested by preclinical data.

Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms such as histamine release.

VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Pharmacokinetics

Absorption

VIVITROL is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month. After IM injection, the naltrexone plasma concentration time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 - 3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.

Maximum plasma concentration (C_{max}) and area under the curve (AUC) for naltrexone and 6β-naltrexol (the major metabolite) following VIVITROL administration are dose proportional. Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 3 to 4-fold higher following administration of a single dose of VIVITROL 380 mg. Steady state is reached at the end of the dosing interval following the first injection. There is minimal accumulation (<15%) of naltrexone or 6β-naltrexol upon repeat administration of VIVITROL.

Distribution

In vitro data demonstrate that naltrexone plasma protein binding is low (21%).

Metabolism

Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6β-naltrexol and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products.

Significantly less 6β-naltrexol is generated following IM administration of VIVITROL compared to administration of oral naltrexone due to a reduction in first-pass hepatic metabolism.

Elimination

Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone.

The elimination half life of naltrexone following VIVITROL administration is 5 to 10 days and is dependent on the erosion of the polymer. The elimination half life of 6β-naltrexol following VIVITROL administration is 5 to 10 days.

Special Populations

Hepatic Impairment: The pharmacokinetics of VIVITROL are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). Dose adjustment is not required in subjects with mild or moderate hepatic impairment. VIVITROL pharmacokinetics were not evaluated in subjects with severe hepatic impairment **(see PRECAUTIONS)**.

Renal Impairment: A population pharmacokinetic analysis indicated mild renal insufficiency (creatinine clearance of 50-80 mL/min) had little or no influence on VIVITROL pharmacokinetics and that no dosage adjustment is necessary **(see PRECAUTIONS)**. VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency **(see PRECAUTIONS)**.

Gender: In a study in healthy subjects (n=18 females and 18 males), gender did not influence the pharmacokinetics of VIVITROL.

Age: The pharmacokinetics of VIVITROL have not been evaluated in the geriatric population.

Race: The effect of race on the pharmacokinetics of VIVITROL has not been studied.

Pediatrics: The pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

Drug-Drug Interactions

Clinical drug interaction studies with VIVITROL have not been performed.

Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics **(see PRECAUTIONS)**.

CLINICAL STUDIES:

The efficacy of VIVITROL in the treatment of alcohol dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol dependent (DSM-IV criteria) outpatients. Subjects were treated with an injection every 4 weeks of VIVITROL 190 mg, VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Psychosocial support was provided to all subjects in addition to medication.

Subjects treated with VIVITROL 380 mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Heavy drinking was defined as self-report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients. Among the subset of patients (n=53, 8% of the total study population) who abstained completely from drinking during the week prior to the first dose of medication, compared with placebo-treated patients, those treated with VIVITROL 380 mg had greater reductions in the number of drinking days and the number of heavy drinking days. In this subset, patients treated with VIVITROL were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment. The same treatment effects were not evident among the subset of patients (n=571, 92% of the total study population) who were actively drinking at the time of treatment initiation.

INDICATIONS AND USAGE:

VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL.

Patients should not be actively drinking at the time of initial VIVITROL administration.

Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

CONTRAINDICATIONS:

VIVITROL is contraindicated in:

- Patients receiving opioid analgesics **(see PRECAUTIONS)**.
- Patients with current physiologic opioid dependence **(see WARNINGS)**.
- Patients in acute opiate withdrawal **(see WARNINGS)**.
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids.
- Patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent.

WARNINGS:

Hepatotoxicity

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Eosinophilic pneumonia

In clinical trials with VIVITROL, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization, and resolved after treatment with antibiotics and corticosteroids. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered **(see ADVERSE REACTIONS)**. Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia. Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics.

Unintended Precipitation of Opioid Withdrawal

To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting VIVITROL treatment. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge test should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of VIVITROL.

Opioid Overdose Following an Attempt to Overcome Opiate Blockade

VIVITROL is not indicated for the purpose of opioid blockade or the treatment of opiate dependence. Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life-endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade **(see INFORMATION FOR PATIENTS)**.

There is also the possibility that a patient who had been treated with VIVITROL will respond to lower doses of opioids than previously used. This could result in potentially life-threatening opioid intoxication (respiratory compromise

manifestations appear, treatm[illegible]
ld be discontinued and appropri[illegible]

ly rarely been reported to cause
e possibility of this occurring
cularly when treating patients
alance. Periodic monitoring of
dvisable in patients receiving

lium content is 4.51 mEq (103.6
. This should be considered whe
ng restricted salt intake.
lin, an allergic reaction, includi
r during TIMENTIN adminis
ersensitive individual.
perinfections with mycotic or
kept in mind, particularly dur
superinfections occur, appropri
n.

TIN in the absence of a pro
acterial infection or a prophyla
provide benefit to the patient
e development of drug-resista

ents: Patients should be co
gs, including TIMENTIN, shou
rial infections. They do not trea
mmon cold). When TIMENTIN
rial infection, patients should
mon to feel better early in the
ation should be taken exactly
or not completing the full co
se the effectiveness of the imm
ease the likelihood that bacteri
will not be treatable by TIMEN
rugs in the future.
roblem caused by antibiotics
antibiotic is discontinued,
tment with antibiotics, patient
dy stools (with or without
as late as 2 or more months
se of the antibiotic. If this o
heir physician as soon as p
teractions: As with other p
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administration can result in
e aminoglycoside.
th the renal tubular secreti
asing serum concentrations
of the antibiotic.
other antibiotics, ticar
assium may affect the gut
reabsorption and reduced effi
progesterone contraceptives
of ticarcillin may produce
pseudoproteinuria) with the
ylic acid and boiling test,
d nitric acid test. The brom
reagent strip test has been

acid in TIMENTIN may cau
and albumin by red cell
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esis, Impairment of
n animals have not been
nic potential. However, resu
n in vitro using bacteria (A
mosomal effects in vitro in
o in mouse bone marrow
t TIMENTIN is without

production studies have b
s up to 1,050 mg/kg/day
impaired fertility or harm
There are, however, no
dies in pregnant women.
dies are not always predict
should be used during pre

own whether this drug is e
many drugs are excreted
exercised when TIMENTI
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effectiveness of TIMENTI
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itional efficacy, safety,
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patients. There are insu
of TIMENTIN in pediat
r for the treatment of se
ediatric population where
is *H. influenzae* type b
ngeal seeding from a
eningitis is suspected
ho require prophylaxis
infection, an alternat
l efficacy in this setting

of clinical studies
ermine whether subject
y from younger subjects
h at least one dose of

NTIN, 67.5% were <65 years old, and 32.5% were ≥65
ld. No overall differences in safety or efficacy were
ed between these subjects and younger subjects, and
eported clinical experience have not identified differ-
in responses between the elderly and younger pa-
but a greater sensitivity of some older individuals
be ruled out.
rug is known to be substantially excreted by the kid-
nd the risk of toxic reactions to this drug may be
in patients with impaired renal function. Because
patients are more likely to have decreased renal
on, care should be taken in dose selection, and it may
ful to monitor renal function (see DOSAGE and AD-
STRATION).
NTIN contains 103.6 mg (4.51 mEq) of sodium per
of TIMENTIN. At the usual recommended doses, pa-
would receive between 1,285 and 1,927 mg/day (56
4 mEq) of sodium. The geriatric population may re-
with a blunted natriuresis to salt loading. This may
inically important with regard to such diseases as con-
ve heart failure.

VERSE REACTIONS

ith other penicillins, the following adverse reactions
occur:
ensitivity Reactions: Skin rash, pruritus, urticaria,
algia, myalgia, drug fever, chills, chest discomfort, er-
ma multiforme, toxic epidermal necrolysis, Stevens-
son syndrome, and anaphylactic reactions.
al Nervous System: Headache, giddiness, neuromus-
hyperirritability, or convulsive seizures.
intestinal Disturbances: Disturbances of taste and
stomatitis, flatulence, nausea, vomiting and diar-
epigastric pain, and pseudomembranous colitis have
reported. Onset of pseudomembranous colitis symp-
may occur during or after antibiotic treatment. (See
ARNINGS.)
ic and Lymphatic Systems: Thrombocytopenia, leuko-
neutropenia, eosinophilia, reduction of hemoglobin or
matocrit, and prolongation of prothrombin time and
ding time.
normalities of Hepatic and Renal Function Tests: Ele-
of serum aspartate aminotransferase (SGOT), serum
ine aminotransferase (SGPT), serum alkaline phospha-
serum LDH, serum bilirubin. There have been reports
ransient hepatitis and cholestatic jaundice—as with
e other penicillins and some cephalosporins. Elevation
erum creatinine and/or BUN, hypernatremia, reduction
erum potassium, and uric acid.
l Reactions: Pain, burning, swelling, and induration
the injection site and thrombophlebitis with intravenous
ministration.
ailable safety data for pediatric patients treated with
MENTIN demonstrate a similar adverse event profile to
observed in adult patients.

RUG ABUSE AND DEPENDENCE

ither abuse of nor dependence on TIMENTIN has been
ported.

VERDOSAGE

with other penicillins, neurotoxic reactions may arise
en very high doses of TIMENTIN are administered, es-
ially in patients with impaired renal function. (See
ARNINGS and ADVERSE REACTIONS—Central Ner-
us System.)
case of overdosage, discontinue TIMENTIN, treat symp-
matically, and institute supportive measures as required.
icarcillin may be removed from circulation by hemodialy-
. The molecular weight, degree of protein binding, and
harmacokinetic profile of clavulanic acid, together with in-
rmation from a single patient with renal insufficiency all
ggest that this compound may also be removed by hemo-
lysis.

OSAGE AND ADMINISTRATION

MENTIN should be administered by intravenous infusion
30 min.).
dults: The usual recommended dosage for systemic and
inary tract infections for average (60 kg) adults is
1 grams TIMENTIN (3.1-gram vial containing 3 grams
icarcillin and 100 mg clavulanic acid) given every 4 to 6
ours. For gynecologic infections, TIMENTIN should be ad-
inistered as follows: Moderate infections, 200 mg/kg/day
divided doses every 6 hours, and for severe infections,
00 mg/kg/day in divided doses every 4 hours. For patients
eighing less than 60 kg, the recommended dosage is 200 to
00 mg/kg/day, based on ticarcillin content, given in divided
ses every 4 to 6 hours.
Pediatric Patients (≥3 months): ***For patients <60 kg:*** In
patients <60 kg, TIMENTIN is dosed at 50 mg/kg/dose
based on the ticarcillin component. TIMENTIN should be
administered as follows: Mild to moderate infections
200 mg/kg/day in divided doses every 6 hours; for severe in-
fections, 300 mg/kg/day in divided doses every 4 hours.
For patients ≥60 kg: For mild to moderate infections,
3.1 grams of TIMENTIN (3 grams of ticarcillin and 100 mg
of clavulanic acid) administered every 6 hours; for severe
infections, 3.1 grams every 4 hours.
Renal Impairment: For infections complicated by renal in-
sufficiency[†], an initial loading dose of 3.1 grams should be
followed by doses based on creatinine clearance and type of
dialysis as indicated below:
[See first table above]

Creatinine clearance mL/min.	Dosage
over 60	3.1 grams every 4 hrs.
30 to 60	2 grams every 4 hrs.
10 to 30	2 grams every 8 hrs.
less than 10	2 grams every 12 hrs.
less than 10 with hepatic dysfunction	2 grams every 24 hrs.
patients on peritoneal dialysis	3.1 grams every 12 hrs.
patients on hemodialysis	2 grams every 12 hrs. supplemented with 3.1 grams after each dialysis

To calculate creatinine clearance[‡] from a serum creatinine value use the following formula:

$$C_{cr} = \frac{(140 - Age)\ (wt.\ in\ kg)}{72 \times S_{cr}\ (mg/100\ mL)}$$

This is the calculated creatinine clearance for adult males; for females it is 15% less.

[‡] Cockcroft, D.W., et al: Prediction of Creatinine Clearance from Serum Creatinine. Nephron 16:31-41, 1976.

STABILITY PERIOD
(31-gram Pharmacy Bulk Package)

Intravenous Solution (ticarcillin concentrations of 10 mg/mL to 100 mg/mL)	Room Temperature 21° to 24°C (70° to 75°F)	Refrigerated 4°C (40°F)
Dextrose Injection 5%, USP	24 hours	3 days
Sodium Chloride Injection 0.9%, USP	24 hours	4 days
Lactated Ringer's Injection, USP	24 hours	4 days
Sterile Water for Injection, USP	24 hours	4 days

[†]The half-life of ticarcillin in patients with renal failure is approximately 13 hours.

Dosage for any individual patient must take into consideration the site and severity of infection, the susceptibility of the organisms causing infection, and the status of the patient's host defense mechanisms.

The duration of therapy depends upon the severity of infection. Generally, TIMENTIN should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 10 to 14 days; however, in difficult and complicated infections, more prolonged therapy may be required.

Frequent bacteriologic and clinical appraisals are necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed. Persistent infections may require treatment for several weeks, and doses smaller than those indicated above should not be used.

In certain infections, involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

INTRAVENOUS ADMINISTRATION
DIRECTIONS FOR PROPER USE OF PHARMACY BULK PACKAGE RECONSTITUTED STOCK SOLUTION MUST BE TRANSFERRED AND FURTHER DILUTED FOR I.V. INFUSION.

The container closure may be penetrated only one time utilizing a suitable sterile transfer device or dispensing set that allows measured distribution of the contents. A sterile substance that must be reconstituted prior to use may require a separate closure entry.

Restrict use of Pharmacy Bulk Packages to an aseptic area such as a laminar flow hood.

Reconstituted contents of the vial should be withdrawn immediately. However, if this is not possible, aliquoting operations must be completed within 4 hours of reconstitution. **Discard the reconstituted stock solution 4 hours after initial entry.**

Add 76 mL of Sterile Water for Injection, USP, or Sodium Chloride Injection, USP, to the 31-gram Pharmacy Bulk Package and shake well. For ease of reconstitution, the diluent may be added in 2 portions. Each 1.0 mL of the resulting concentrated stock solution contains approximately 300 mg of ticarcillin and 10 mg of clavulanic acid.

Intravenous Infusion: The desired dosage should be withdrawn from the stock solution and further diluted to desired volume using the recommended solution listed in the COMPATIBILITY AND STABILITY section (STABILITY PERIOD) to a concentration between 10 mg/mL to 100 mg/mL. The solution of reconstituted drug may then be administered over a period of 30 minutes by direct infusion, or through a Y-type intravenous infusion set. If this method of administration is used, it is advisable to discontinue temporarily the administration of any other solution during the infusion of TIMENTIN.

Stability: For I.V. solutions, see STABILITY PERIOD below.

When TIMENTIN is given in combination with another antimicrobial, such as an aminoglycoside, each drug should be given separately in accordance with the recommended dosage and routes of administration for each drug.

After reconstitution and prior to administration, TIMENTIN, as with other parenteral drugs, should be inspected visually for particulate matter. If this condition is evident, the solution should be discarded.

The color of reconstituted solutions of TIMENTIN normally ranges from light to dark yellow, depending on concentration, duration, and temperature of storage while maintaining label claim characteristics.

COMPATIBILITY AND STABILITY
31-gram Pharmacy Bulk Package
(Dilutions derived from a stock solution of 300 mg/mL)

Aliquots of the reconstituted stock solution at 300 mg/mL are stable for up to 6 hours between 21° and 24°C (70° and 75°F) or up to 72 hours under refrigeration 4°C (40°F). The reconstituted stock solution should be held under refrigeration 4°C (40°F).

If the aliquots of the reconstituted stock solution (300 mg/mL) are held up to 6 hours between 21° and 24°C (70° and 75°F) or up to 72 hours under refrigeration 4°C (40°F) and further diluted to a concentration between 10 mg/mL and 100 mg/mL with any of the diluents listed below, then the following stability periods apply.

[See second table above]

If an aliquot of concentrated stock solution (300 mg/mL) is stored for up to 6 hours between 21° and 24°C (70° and 75°F) and then further diluted to a concentration between 10 mg/mL and 100 mg/mL, solutions of Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Sterile Water for Injection, USP, may be stored frozen –18°C (0°F) for up to 30 days. Solutions prepared with Dextrose Injection 5%, USP, may be stored frozen –18°C (0°F) for up to 7 days. All thawed solutions should be used within 8 hours or discarded. Once thawed, solutions should not be refrozen.

NOTE: TIMENTIN is incompatible with Sodium Bicarbonate.

Unused solutions must be discarded after the time periods listed above.

HOW SUPPLIED

Each 31-gram vial of TIMENTIN contains sterile ticarcillin disodium equivalent to 30 grams ticarcillin and sterile clavulanate potassium equivalent to 1 gram clavulanic acid.
NDC 0029-6579-21 31-gram Pharmacy Bulk Package
TIMENTIN is also supplied as:
NDC 0029-6571-26 3.1-gram Vial
NDC 0029-6571-40 3.1-gram ADD-VANTAGE®[§] Antibiotic Vial

Vials of TIMENTIN should be stored at or below 24°C (75°F).

NDC 0029-6571-31 TIMENTIN, as an iso-osmotic, sterile, nonpyrogenic, frozen solution in GALAXY®[‖] (PL 2040) Plastic Containers—supplied in 100 mL single-dose containers equivalent to 3 grams ticarcillin and clavulanate potassium equivalent to 0.1 gram clavulanic acid.

CLINICAL STUDIES

TIMENTIN has been studied in a total of 296 pediatric patients (excluding neonates and infants less than 3 months) in 6 controlled clinical trials. The majority of patients studied had intra-abdominal infections, and the primary comparator was clindamycin and gentamicin with or without ampicillin. At the end-of-therapy visit, comparable efficacy was reported in the trial arms using TIMENTIN and an appropriate comparator.

TIMENTIN was also evaluated in an additional 408 pediatric patients (excluding neonates and infants less than 3 months) in 3 uncontrolled US clinical trials. Patients were treated across a broad range of presenting diagnoses including: Infections in bone and joint, skin and skin structure, lower respiratory tract, urinary tract, as well as intra-abdominal and gynecologic infections. Patients received TIMENTIN either 300 mg/kg/day (based on the ticarcillin component) divided every 4 hours for severe infection or 200 mg/kg/day (based on the ticarcillin component) divided every 6 hours for mild to moderate infections. The efficacy rates were comparable to those obtained in the controlled trials.

The adverse event profile in these 704 pediatric patients treated with TIMENTIN was comparable to that seen in adult patients.

Continued on next page

Cardizem LA—Cont.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Lovastatin. In a ten-subject study, coadministration of diltiazem (120 mg bid diltiazem SR) with lovastatin resulted in a 3–4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Quinidine. Diltiazem significantly inreases $AUC_{0-\infty}$ of quinidirae by 51%, $T_{1/2}$ by 36%, and decreases it CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

Rifampin. Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP 3A4 inducer should be avoided when possible, and alternative therapy considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

Geriatric Use Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In the hypertension study, the following table presents adverse reactions more common on diltiazem than on placebo (but excluding events with no plausible relationship to treatment), as reported in placebo-controlled hypertension trials in patients receiving a diltiazem hydrochloride extended-release formulation (once-a-day dosing) up to 540 mg.

	Placebo	Diltiazem hydrochloride extended-release	
Adverse Reactions (MedDRA Term)	**n = 120 # pts (%)**	**120–360 mg n = 501 # pts (%)**	**540 mg n = 123 # pts (%)**
Oedema lower limb	4 (3)	24 (5)	10 (8)
Sinus congestion	0 (0)	2 (1)	2 (2)
Rash NOS	0 (0)	3 (1)	2 (2)

In the angina study, the adverse event profile of CARDIZEM LA was consistent with what has been previously described for CARDIZEM LA and other formulations of diltiazem HCl. The most frequent adverse effects experienced by CARDIZEM LA-treated patients were edema lower-limb (6.8%), dizziness (6.4%), fatigue (4.8%), bradycardia (3.6%), first-degree atrioventricular block (3.2%), and cough (2%).

In clinical trials of other diltiazem formulations involving over 3200 patients, the most common events (i.e. greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%) and rash (1.2%).

In addition, the following events have been reported infrequently (less than 2%) in hypertension trials with other diltiazem products:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), nausea, thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus.

Other: Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, ecchymosis, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, neck rigidity, nocturia, osteoarticular pain, pain, polyuria, rhinitis, sexual difficulties, gynecomastia.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

OVERDOSAGE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem eliminiation following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1 mg). If there is no response to vagal blockage, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension Vasopressors (e.g., dopamine or norepinephrine).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

CARDIZEM LA Tablets are an extended release formulation intended for once-a-day administration.

Patients controlled on diltiazem alone or in combination with other medications may be switched to CARDIZEM LA Tablets once-a-day at the nearest equivalent total daily dose. Higher doses of CARDIZEM LA Tablets once-a-day dosage may be needed in some patients [illegible] closely monitored. Subsequent titration [illegible] doses may be necessary and should be [illegible] warranted. There is limited general clinical [illegible] doses above 360 mg, but the safety [illegible] high as 540 mg have been studied in [illegible] cidence of side effects increases as the [illegible] first-degree AV block, dizziness, and sinus [illegible] ing the strongest relationship to dose. [illegible] The tablet should be swallowed whole [illegible] crushed.

Hypertension

Dosage needs to be adjusted by titration [illegible] tient needs. When used as monotherapy [illegible] ing doses are 180 to 240 mg once daily [illegible] patients may respond to lower doses. [illegible] tensive effect is usually observed by 14 days [illegible] apy; therefore, dosage adjustments should [illegible] cordingly. The dosage range studied in [illegible] 120 to 540 mg once daily. The dosage may [illegible] maximum of 540 mg daily.

CARDIZEM LA Tablets should be taken [illegible] time once each day either in the morning [illegible] time of dosing should be considered when [illegible] justments based on trough effects.

Angina

Dosage for the treatment of angina should [illegible] based on response. The initial dose of 180 [illegible] may be increased at intervals of 7 - 14 days [illegible] sponse is not obtained. CARDIZEM LA doses [illegible] appear to confer no additional benefit. [illegible] CARDIZEM LA can be given once daily, [illegible] ning or in the morning.

Concomitant Use with Other Cardiovascular [illegible]

1. **Sublingual NTG.** May be taken as re[illegible] acute anginal attacks during Diltiazem [illegible] Extended release therapy.
2. **Prophylactic Nitrate Therapy.** Diltiazem [illegible] Extended Release Tablets may be safely [illegible] with short-and and long-acting nitrates [illegible]
3. **Beta-blockers.** (See WARNINGS and PRE[illegible])
4. **Antihypertensives.** CARDIZEM LA has [illegible] tihypertensive effect when used with other [illegible] sive agents. Therefore, the dosage [illegible] Hydrochloride Extended Release Tablets [illegible] tant antihypertensives may need to be [illegible] adding one to the other.

HOW SUPPLIED

CARDIZEM LA is supplied as white, capsule [illegible] debossed with "B" on one side and the [illegible] (mg) on the other.

	NDC 60598-xxx-xx
Strength	**Qty 30**
120 mg	120-30
180 mg	121-30
240 mg	122-30
300 mg	123-30
360 mg	124-30
420 mg	125-30

Storage conditions: Store at 25°C (77°F) [illegible] mitted to 15-30°C (59-86°F) [illegible] Controlled Room Temperature [illegible] Avoid excessive humidity [illegible] peratures above 30°C [illegible]

Dispense in tight, light resistant container [illegible] USP.

® Cardizem is a registered trademark of [illegible] Biovail Laboratories International SRL [illegible]

Manufactured by:
Biovail Corporation
Mississauga, ON, L5N 8M5
Canada
Distributed by:
Kos Pharmaceuticals, Inc.
Cranbury, NJ 08512 USA
Made in Canada
LB0024-06
400276/0406

Shown in Product Identification Guide

NIASPAN®

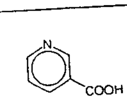
[*niă-span*]
(niacin extended-release tablets)
Tablet, Extended Release

℞ Only

DESCRIPTION

NIASPAN® (niacin extended-release tablets) [illegible] niacin, which at therapeutic doses is an anti[illegible] agent. Niacin (nicotinic acid, or 3-pyridine[illegible]) a white, crystalline powder, very soluble in [illegible] following structural formula:

[See structural formula at top of next column]



$C_6H_5NO_2$ M.W. = 123.11

NIASPAN® is an unscored, medium-orange [illegible] tablet for oral administration and is available [illegible] containing 500, 750, and 1000 [illegible] tablets also contain the inactive [illegible] povidone, stearic acid, and polye[illegible] following coloring agents: FD&C [illegible] FCF Aluminum Lake, synthetic [illegible] and titanium dioxide.

[illegible] PHARMACOLOGY

[illegible] in the body after conversion [illegible] dinucleotide (NAD) in the NAD c[illegible] but not nicotinamide) in gram d[illegible] rol (TC), low-density lipoprotei[illegible] triglycerides (TG), and increases [illegible] cholesterol (HDL-C). The magnitu[illegible] lipoprotein responses may be infl[illegible] type of underlying lipid abnorm[illegible] HDL-C is associated with an in[illegible] (Apo A-I) and a shift in the d[illegible] tions. These shifts include an ir[illegible] ratio, and an elevation in lipop[illegible] particle containing only Apo A-I) [illegible] decreases serum levels of apolipo[illegible] major protein component of [illegible] protein (VLDL) and LDL fractions [illegible] of LDL independently associ[illegible] addition, preliminary report[illegible] favorable LDL particle size tr[illegible] clinical relevance of this effect r[illegible] The effect of niacin-induced ch[illegible] cardiovascular morbidity or [illegible] without pre-existing coronary d[illegible] ished.

[illegible] clinical studies have demonst[illegible] TC, LDL-C, and Apo B prom[illegible] Similarly, decreased levels of H[illegible] the development of [illegible] [illegible] investigations have estab[illegible] morbidity and mortality vary [illegible] and LDL-C, and inversely w[illegible]

[illegible] cholesterol-enriched triglycer[illegible] VLDL, intermediate-den[illegible] their remnants, can also prom[illegible] plasma TG are frequently fou[illegible] levels and small LDL particles [illegible] non-lipid metabolic risk fa[illegible] (CHD). As such, total plas[illegible] been shown to be an indepenc[illegible] thermore, the independent [illegible] lowering TG on the risk of cor[illegible] morbidity and mortality has not [illegible]

[illegible] of Action

[illegible] by which niacin alters li[illegible] defined. It may involve severa[illegible] inhibition of release of free fatty [illegible] increased lipoprotein lipase [illegible] the rate of chylomicron triglyc[illegible] niacin decreases the rate of h[illegible] LDL and does not appear t[illegible] sterols, or bile acids.

[illegible]tics/Metabolism

[illegible] rapidly and extensively abso[illegible] when administered orall[illegible] and reduce the risk of gast[illegible] tion of NIASPAN® wit[illegible] recommended.

[illegible] bioavailability studies hav[illegible] and 1000mg tablet streng[illegible] the 500mg and 750mg [illegible] equivalent.

[illegible] radiolabeled niacin in n[illegible] metabolites concentrate in the [illegible]

[illegible] pharmacokinetic profile of niacin [illegible] extensive first-pass metabo[illegible] specific. In humans, one [illegible] step with glycine t[illegible] then excreted in the [illegible] small amount of reversibl[illegible] other pathway results in [illegible] adenine dinucleotide (NAD [illegible] formed as a precurs[illegible] NADP. Nicotinamide is [illegible] methylnicotinamide (MN[illegible] MNA is further metab[illegible] methyl-2-pyridone-5-ca[illegible] pyridone-5-carboxamide [illegible] predominate over [illegible] at hyperlipidemia [illegible] able, which explains [illegible] niacin dose and plasm[illegible] NIASPAN® admi[illegible] does not have hypoli[illegible] these metabolites is u[illegible]

ed Clinical Studies

rom Baseline (25th

)

l)

4)

was 4 weeks.

onse

hange from Baseline

	TG	
	M	F
	-3	-9
	-10	-20
	-17	-28
	-30	-36

Low HDL-C

Change from Baseline

Lp(a)†	Apo B†	(Apo
8	106	
-20	-9	

oid parameters shown

eline

Lovastatin

	n*	Dose (mg)
dL	61	
	56	20
	56	40
	54	40
	53	40

seline

Lovastatin

	n*	Dose (mg)
/dL	61	
%	56	20
%	56	40
%	54	40
%	53	40

with a history of myocardial
erolemia, niacin is indicated
rent nonfatal myocardial
with a history of coronary
ypercholesterolemia,
ile acid binding resin,
or promote regression

in combination with a
cated as an adjunct to diet
and LDL-C levels in adults

ary hypercholesterolemia (Type IIa; Table 11), and the response to an appropriate diet, or diet plus exercise therapy, has been inadequate.

is also indicated as adjunctive therapy for treatment of adult patients with very high serum triglycerides (Types IV and V hyperlipidemia; Table 11) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum TG levels over 2000 mg/dL and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia; Table 11). Patients who consistently have total serum or plasma TG below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with TG under 1000 mg/dL may, through dietary or alcohol indiscretion, convert to a Type V pattern with massive TG elevations accompanied by fasting chylomicronemia, but the influence of niacin therapy on risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma TG but who have normal levels of VLDL-C. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[9]

[See table 11 above]

If LDL-C goal has been achieved, if the TG is still 200 mg/dL, non-HDL-C (TC minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Table 11. Classification of Hyperlipoproteinemias

Lipoproteins Elevated	Lipid Elevations Major	Minor
Chylomicrons	TG	↑→TC
LDL	TC	–
LDL, VLDL	TC	TG
IDL	TC/TG	–
VLDL	TG	↑→TC
Chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein
↑ = increased or no change

CONTRAINDICATIONS

NIASPAN® is contraindicated in patients with a known hypersensitivity to niacin or any component of this medication, significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding.

WARNINGS

NIASPAN® preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. Patients switching from immediate-release niacin to niacin therapy with NIASPAN® should be initiated at low doses (i.e., 500mg qhs) and the NIASPAN® dose should be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

Hepatic Dysfunction

Rare cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

NIASPAN® should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of NIASPAN®.

Niacin preparations, like some other lipid-lowering therapies, have been associated with abnormal liver tests. In placebo-controlled clinical trials involving titration to 2000mg, NIASPAN® doses ranging from 500 to 3000mg, patients received NIASPAN® for a mean duration of 17 weeks. A patient with normal serum transaminase levels at baseline experienced elevations to more than three times the upper limit of normal (ULN) during treatment with NIASPAN®. In these studies, fewer than 1% (2/245) of NIASPAN® patients discontinued due to transaminase elevations greater than 2 times the ULN.

In safety and efficacy studies with a combination tablet of NIASPAN® and lovastatin involving titration to final dose (expressed as mg of niacin/mg of lovastatin) of 1000/40mg to 2500mg/40mg, ten of 1028 patients (1.0%) developed reversible elevations in AST/ALT to more than three times the upper limit of normal (ULN). Three of ten elevations occurred at doses outside the recommended dosing range of 2000mg/40mg; no patient receiving 1000mg/20mg had elevations in AST/ALT.

In placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear related to treatment duration; elevations in AST levels appeared to be dose related. Transaminase elevations were reversible upon discontinuation of NIASPAN®.

Liver tests should be performed on all patients during therapy with NIASPAN®. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Skeletal Muscle

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and HMG-CoA reductase inhibitors. In clinical studies with a combination tablet of NIASPAN® and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with doses up to 2000mg of NIASPAN® and 40mg of lovastatin daily for periods up to 2 years. **Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and NIASPAN® should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.** Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS

General

Before instituting therapy with NIASPAN®, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during NIASPAN® therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when NIASPAN® is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

NIASPAN® has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000mg). In addition, NIASPAN® has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when NIASPAN® is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

In placebo-controlled trials, NIASPAN® has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. NIASPAN® is contraindicated in patients with significant or unexplained hepatic dysfunction (see **CONTRAINDICATIONS** and **WARNINGS**) and should be used with caution in patients with renal dysfunction.

Information for Patients

Patients should be advised:

- to take NIASPAN® at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended;
- to carefully follow the prescribed dosing regimen, including the recommended titration schedule, in order to minimize side effects (see **DOSAGE AND ADMINISTRATION**);

Continued on next page

Table 8. TG median percent change from baseline

Week	Combination tablet of NIASPAN® and lovastatin			NIASPAN®			Lovastatin		
	n*	Dose (mg/mg)	TG	n*	Dose (mg)	TG	n*	Dose (mg)	TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

*n = number of patients remaining in trial at each time point

Table 9. Lp(a) median percent change from baseline

Week	Combination tablet of NIASPAN® and lovastatin			NIASPAN®			Lovastatin		
	n*	Dose (mg/mg)	Lp(a)	n*	Dose (mg)	Lp(a)	n*	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	60	-	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

*n = number of patients remaining in trial at each time point

Table 10. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

†CHD, coronary heart disease
††Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
†††Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Asacol—Cont.

leading to withdrawal from **Asacol** tablets included (each in one patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache; rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild indigestion and cramping; headache, nausea, aching, vomiting, muscle cramps, a stuffy head, plugged ears, and fever.

Adverse events occurring in **Asacol**-treated patients at a frequency of 2% or greater in the two short-term, double-blind, placebo-controlled trials mentioned above are listed in Table 1 below. Overall, the incidence of adverse events seen with **Asacol** tablets was similar to placebo.

Table 1
Frequency (%) of Common Adverse Events Reported in Ulcerative Colitis Patients Treated with **Asacol** Tablets or Placebo in Short-Term (6-Week) Double-Blind Controlled Studies

	Percent of Patients with Adverse Events	
Event	Placebo (n = 87)	**Asacol** tablets (n = 152)
Headache	36	35
Abdominal pain	14	18
Eructation	15	16
Pain	8	14
Nausea	15	13
Pharyngitis	9	11
Dizziness	8	8
Asthenia	15	7
Diarrhea	9	7
Back pain	5	7
Fever	8	6
Rash	3	6
Dyspepsia	1	6
Rhinitis	5	5
Arthralgia	3	5
Hypertonia	3	5
Vomiting	2	5
Constipation	1	5
Flatulence	7	3
Dysmenorrhea	3	3
Chest pain	2	3
Chills	2	3
Flu syndrome	2	3
Peripheral edema	2	3
Myalgia	1	3
Sweating	1	3
Colitis exacerbation	0	3
Pruritus	0	3
Acne	1	2
Increased cough	1	2
Malaise	1	2
Arthritis	0	2
Conjunctivitis	0	2
Insomnia	0	2

Of these adverse events, only rash showed a consistently higher frequency with increasing **Asacol** dose in these studies.

In a 6-month placebo-controlled maintenance trial involving 264 patients, 177 of whom were randomized to **Asacol** tablets, six (3.4%) of the **Asacol** patients discontinued **Asacol** therapy because of adverse events, as compared to four (4.6%) of the placebo patients. Adverse reactions leading to withdrawal from **Asacol** tablets included (each in one patient): anxiety; headache; pruritus; decreased libido; rheumatoid arthritis; and stomatitis and asthenia.

In the 6-month placebo-controlled maintenance trial, the incidence of adverse events seen with **Asacol** tablets was similar to that seen with placebo. In addition to events listed in Table 1, the following adverse events occurred in **Asacol**-treated patients at a frequency of 2% or greater in this study: abdominal enlargement, anxiety, bronchitis, ear disorder, ear pain, gastroenteritis, gastrointestinal hemorrhage, infection, joint disorder, migraine, nervousness, paresthesia, rectal disorder, rectal hemorrhage, sinusitis, stool abnormalities, tenesmus, urinary frequency, vasodilation, and vision abnormalities.

In 3342 patients in uncontrolled clinical studies, the following adverse events occurred at a frequency of 5% or greater and appeared to increase in frequency with increasing dose: asthenia, fever, flu syndrome, pain, abdominal pain, back pain, flatulence, gastrointestinal bleeding, arthralgia, and rhinitis.

In addition to the adverse events listed above, the following events have been reported in clinical studies, literature reports, and postmarketing use of products which contain (or have been metabolized to) mesalamine. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness or potential causal connection to mesalamine:

Body as a Whole: Neck pain, facial edema, edema, lupus-like syndrome, drug fever (rare).

Cardiovascular: Pericarditis (rare), myocarditis (rare).

Gastrointestinal: Anorexia, pancreatitis, gastritis, increased appetite, cholecystitis, dry mouth, oral ulcers, perforated peptic ulcer (rare), bloody diarrhea. There have been rare reports of hepatotoxicity including, jaundice, cholestatic jaundice, hepatitis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. Asymptomatic elevations of liver enzymes which usually resolve during continued use or with discontinuation of the drug have also been reported. One case of Kawasaki-like syndrome which included changes in liver enzymes was also reported.

Hematologic: Agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Musculoskeletal: Gout.

Nervous: Depression, somnolence, emotional lability, hyperesthesia, vertigo, confusion, tremor, peripheral neuropathy (rare), transverse myelitis (rare), Guillain-Barré syndrome (rare).

Respiratory/Pulmonary: Eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis.

Skin: Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, urticaria.

Special Senses: Eye pain, taste perversion, blurred vision, tinnitus.

Urogenital: Renal Failure (rare), interstitial nephritis, minimal change nephropathy (See also Renal subsection in PRECAUTIONS). Dysuria, urinary urgency, hematuria, epididymitis, menorrhagia.

Laboratory Abnormalities: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated GGT, elevated LDH, elevated bilirubin, elevated serum creatinine and BUN.

DRUG ABUSE AND DEPENDENCY

Abuse: None reported.

Dependency: Drug dependence has not been reported with chronic administration of mesalamine.

OVERDOSAGE

Two cases of pediatric overdosage have been reported. A 3-year-old male who ingested 2 grams of **Asacol** tablets was treated with ipecac and activated charcoal; no adverse events occurred. Another 3-year-old male, approximately 16 kg, ingested an unknown amount of a maximum of 24 grams of **Asacol** crushed in solution (i.e., uncoated mesalamine); he was treated with orange juice and activated charcoal, and experienced no adverse events. In dogs, single doses of 6 grams of delayed-release **Asacol** tablets resulted in renal papillary necrosis but were not fatal. This was approximately 12.5 times the recommended human dose (based on a dose of 2.4 g/day in a 50 kg person). Single oral doses of uncoated mesalamine in mice and rats of 5000 mg/kg and 4595 mg/kg, respectively, or of 3000 mg/kg in cynomolgus monkeys, caused significant lethality.

DOSAGE AND ADMINISTRATION

For the treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400-mg tablets to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.

For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 1.6 grams daily, in divided doses. Treatment duration in the prospective, well-controlled trial was 6 months.

HOW SUPPLIED

Asacol tablets are available as red-brown, capsule-shaped tablets containing 400 mg mesalamine and imprinted "Asacol NE" in black.

NDC 0149-0752-15 Bottle of 180

Store at controlled room temperature 20°-25°C (68°-77°F) [See USP].

Procter & Gamble Pharmaceuticals
Cincinnati, OH 45202
under license from Medeva Pharma Schweiz AG
registered trademark owner.
Made in Germany, D-64331 Weiterstadt
U.S. Patent Nos. 5,541,170 and 5,541,171
REVISED September 2006

Shown in Product Identification Guide, page 329

DANTRIUM®

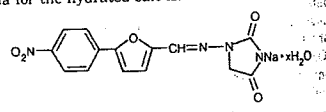
℞

[dān-trē-um]
(dantrolene sodium)
Capsules

Dantrium (dantrolene sodium) has a potential for hepatotoxicity, and should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and non-fatal) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to **Dantrium** for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age, and in patients taking other medication(s) in addition to **Dantrium**(dantrolene sodium). **Dantrium** should be used only in conjunction with appropriate monitoring of hepatic function including frequent determination of SGOT or SGPT. If no observable benefit is derived from the administration of **Dantrium** after a total of 45 days, therapy should be discontinued. The lowest possible effective dose for the individual patient should be prescribed.

DESCRIPTION

The chemical formula of **Dantrium**(dantrolene sodium) is hydrated 1 - [[[5 - (4 - nitrophenyl) - 2 - furanyl]methylene] amino]-2, 4-imidazolidinedione sodium salt. It is an orange powder, slightly soluble in water, but due to its slightly acidic nature the solubility increases somewhat in alkaline solution. The anhydrous salt has a molecular weight of 336. The hydrated salt contains approximately 15% water (3 2 moles) and has a molecular weight of 399. The structural formula for the hydrated salt is:



Dantrium is supplied in capsules of 25 mg, 50 mg, and 100 mg.

Inactive Ingredients: Each capsule contains edible black ink, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

In isolated nerve-muscle preparation, **Dantrium** has been shown to produce relaxation by affecting the contractile response of the skeletal muscle at a site beyond the myoneural junction, directly on the muscle itself. In skeletal muscle, **Dantrium** dissociates the excitation-contraction coupling, probably by interfering with the release of Ca^{++} from the sarcoplasmic reticulum. This effect appears to be more pronounced in fast muscle fibers as compared to slow ones. It generally affects both. A central nervous system effect occurs, with drowsiness, dizziness, and generalized weakness occasionally present. Although **Dantrium** does not appear to directly affect the CNS, the extent of its indirect effects is unknown. The absorption of **Dantrium** after oral administration in humans is incomplete and slow but consistent, and dose-related blood levels are obtained. The duration and intensity of skeletal muscle relaxation is related to dosage and blood levels. The mean biologic half-life of **Dantrium** in adults is 8.7 hours after a 100-mg dose. Specific metabolic pathways in the degradation and elimination of **Dantrium** in human subjects have been established. Metabolic patterns are similar in adults and pediatric patients. In addition to the parent compound, dantrolene, which is found in measurable amounts in blood and urine, the major metabolites noted in body fluids are the 5-hydroxy and the acetamido analog. Since **Dantrium** is probably detoxified by hepatic microsomal enzymes, enhancement of its metabolism by other drugs is possible. However, neither phenobarbital nor diazepam appears to affect Dantrium metabolism.

Clinical experience in the management of fulminant hyperthermia, as well as experiments conducted in malignant hyperthermia susceptible swine, have revealed that the administration of intravenous dantrolene, combined with indicated supportive measures, is effective in reversing the hypermetabolic process of malignant hyperthermia. Known differences between human and swine malignant hyperthermia are minor. The prophylactic administration of oral or intravenous dantrolene to malignant hyperthermia susceptible swine will attenuate or prevent the development of signs of malignant hyperthermia in a manner dependent upon the dosage of dantrolene administered and the intensity of the malignant hyperthermia triggering stimulus. Limited clinical experience with the administration of oral dantrolene to patients susceptible to malignant hyperthermia susceptible, when combined with clinical experience in the use of intravenous dantrolene in the treatment of malignant hyperthermia and data derived from the above cited animal model experiments, suggest that oral dantrolene will also attenuate or prevent the development of signs of human malignant hyperthermia provided that currently accepted practices in the management of such patients are adhered to (see **INDICATIONS AND USAGE**); intravenous dantrolene should also be available for use should the signs of malignant hyperthermia appear.

INDICATIONS AND USAGE

In Chronic Spasticity: **Dantrium** is indicated in the manifestations of clinical spasticity resulting from upper motor neuron disorders (e.g., spinal cord injury, cerebral palsy, or multiple sclerosis). It is of particular benefit to the patient whose functional rehabilitation is retarded by the sequelae of spasticity. Such patients have presumably reversible spasticity where relief of spasticity will aid in restoring residual function. **Dantrium** is indicated in the treatment of skeletal muscle spasticity resulting from rheumatic disorders.

If improvement occurs, it will ordinarily occur during dosage titration (see **DOSAGE AND ADMINISTRATION**), and will be manifested by a decrease in the degree of spasticity and the ability to resume a daily routine quite attainable without **Dantrium**.

Occasionally, subtle but meaningful improvement in spasticity may occur with **Dantrium** therapy. In such

SORIATANE®

℞

[sōr-ĭ-ă-tān]
(acitretin)
CAPSULES

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS:
Soriatane must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Soriatane also must not be used by females who may not use reliable contraception while undergoing treatment and for at least 3 years following discontinuation of treatment. Acitretin is a metabolite of etretinate (Tegison®), and major human fetal abnormalities have been reported with the administration of acitretin and etretinate. Potentially, any fetus exposed can be affected.
Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a significantly longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with Soriatane or for 2 months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification.
Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison.
Major human fetal abnormalities associated with acitretin and/or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of hip, ankle and forearm, low-set ears, high palate, decreased cranial volume, cardiovascular malformation and alterations of the skull and cervical vertebrae.
Soriatane should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity.
Important Information for Women of Childbearing Potential:
Soriatane should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.
Females of reproductive potential must not be given a prescription for Soriatane until pregnancy is excluded. Soriatane is contraindicated in females of reproductive potential unless the patient meets ALL of the following conditions:

- Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Soriatane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue Soriatane therapy. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Soriatane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.
- Must have selected and have committed to use 2 effective forms of contraception (birth control) simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly postmenopausal.
- Patients must use 2 effective forms of contraception (birth control) simultaneously for at least 1 month prior to initiation of Soriatane therapy, during Soriatane therapy, and for at least 3 years after discontinuing Soriatane therapy. A Soriatane Patient Referral Form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed.

Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide.
Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception (birth control) simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[1] Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*
Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).

- Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to Soriatane, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows:
Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least 3 years after stopping treatment with acitretin, based on the following considerations:

- In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within 2 months, assuming a mean elimination half-life of 49 hours.
- In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol,
  - ♦greater than 98% of the etretinate formed would be eliminated in 2 years, assuming a mean elimination half-life of 120 days.
  - ♦greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168 days.

  However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.[2]
- Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred *after* the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.
  - ♦There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred *after* the last dose of etretinate (103 cases), acitretin (126) or both (9). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 years after the last dose but there were no reports of birth defects in these cases.
  - ♦There is also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia, and stillbirth).
  - ♦Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison. Tegison is no longer marketed in the US; for information, call Connetics at 1-888-500-DERM (3376).
  - ♦Patients should not donate blood during and for at least 3 years following the completion of Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

Important Information For Males Taking Soriatane:

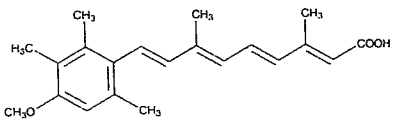
- Patients should not donate blood during and for at least 3 years following Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.
- Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:
  There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome)[3].

For All Patients: A SORIATANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME SORIATANE IS DISPENSED, AS REQUIRED BY LAW.

[See table at top of next page]

DESCRIPTION

Soriatane (acitretin), a retinoid, is available in 10 mg and 25 mg gelatin capsules for oral administration. Chemically, acitretin is all-*trans*-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid. It is a metabolite of etretinate and is related to both retinoic acid and retinol (vitamin A). It is a yellow to greenish-yellow powder with a molecular weight of 326.44. The structural formula is:



Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides).

Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

CLINICAL PHARMACOLOGY

The mechanism of action of Soriatane is unknown.

Pharmacokinetics: *Absorption:* Oral absorption of acitretin is optimal when given with food. For this reason, acitretin was given with food in all of the following studies. After administration of a single 50 mg oral dose of acitretin to 18 healthy subjects, maximum plasma concentrations ranged from 196 to 728 ng/mL (mean 416 ng/mL) and were achieved in 2 to 5 hours (mean 2.7 hours). The oral absorption of acitretin is linear and proportional with increasing doses from 25 to 100 mg. Approximately 72% (range 47% to 109%) of the administered dose was absorbed after a single 50 mg dose of acitretin was given to 12 healthy subjects.

Distribution: Acitretin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism (see *Pharmacokinetic Drug Interactions: Ethanol*): Following oral absorption, acitretin undergoes extensive metabolism and interconversion by simple isomerization to its 13-*cis* form (*cis*-acitretin). The formation of *cis*-acitretin relative to parent compound is not altered by dose or fed/fast conditions of oral administration of acitretin. Both parent compound and isomer are further metabolized into chain-shortened breakdown products and conjugates, which are excreted. Following multiple-dose administration of acitretin, steady-state concentrations of acitretin and *cis*-acitretin in plasma are achieved within approximately 3 weeks.

Elimination: The chain-shortened metabolites and conjugates of acitretin and *cis*-acitretin are ultimately excreted in the feces (34% to 54%) and urine (16% to 53%). The terminal elimination half-life of acitretin following multiple-dose administration is 49 hours (range 33 to 96 hours), and that of *cis*-acitretin under the same conditions is 63 hours (range 28 to 157 hours). The accumulation ratio of the parent compound is 1.2; that of *cis*-acitretin is 6.6.

Special Populations: *Psoriasis:* In an 8-week study of acitretin pharmacokinetics in patients with psoriasis, mean steady-state trough concentrations of acitretin increased in a dose proportional manner with dosages ranging from 10 to 50 mg daily. Acitretin plasma concentrations were nonmeasurable (<4 ng/mL) in all patients 3 weeks after cessation of therapy.

Elderly: In a multiple-dose study in healthy young (n = 6) and elderly (n = 8) subjects, a two-fold increase in acitretin plasma concentrations were seen in elderly subjects, although the elimination half-life did not change.

Renal Failure: Plasma concentrations of acitretin were significantly (59.3%) lower in end-stage renal failure subjects (n = 6) when compared to age-matched controls, following single 50 mg oral doses. Acitretin was not removed by hemodialysis in these subjects.

Pharmacokinetic Drug Interactions (see also boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS: *Drug Interactions*): In studies of in vivo pharmacokinetic drug interactions, no interaction was seen between acitretin and cimetidine, digoxin, phenprocoumon or glyburide.

Ethanol: Clinical evidence has shown that etretinate (a retinoid with a much longer half-life, see below) can be formed with concurrent ingestion of acitretin and ethanol. In a two-way crossover study, all 10 subjects formed etretinate with concurrent ingestion of a single 100 mg oral dose of acitretin during a 3-hour period of ethanol ingestion (total ethanol, approximately 1.4 g/kg body weight). A mean peak etretinate concentration of 59 ng/mL (range 22 to 105 ng/mL) was observed, and extrapolation of AUC values indicated that the formation of etretinate in this study was comparable to a single 5 mg oral dose of etretinate. There was no detectable formation of etretinate when a single 100 mg oral dose of acitretin was administered without concurrent ethanol ingestion, although the formation of etretinate without concurrent ethanol ingestion cannot be excluded (see boxed CONTRAINDICATIONS AND WARNINGS). Of 93 evaluable psoriatic patients on acitretin therapy in several foreign studies (10 to 80 mg/day), 16% had measurable etretinate levels (>5 ng/mL).

Etretinate has a much longer elimination half-life compared to that of acitretin. In one study the apparent mean terminal half-life after 6 months of therapy was approximately 120 days (range 84 to 168 days). In another study of 47 patients treated chronically with etretinate, 5 had detectable serum drug levels (in the range of 0.5 to 12 ng/mL) 2.1 to 2.9 years after therapy was discontinued. The long half-life appears to be due to storage of etretinate in adipose tissue.

Progestin-only Contraceptives: It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[1] Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*

CLINICAL STUDIES

In two double-blind placebo controlled studies, Soriatane was administered once daily to patients with severe psoriasis (ie, covering at least 10% to 20% of the body surface area). At 8 weeks (see Table 1) patients treated in Study A with 50 mg Soriatane per day showed significant improvements ($p \leq 0.05$) relative to baseline and to placebo in the physician's global evaluation and in the mean ratings of severity of psoriasis (scaling, thickness, and erythema). In study B, differences from baseline and from placebo were statistically significant ($p \leq 0.05$) for all variables at both the 25 mg and 50 mg doses; it should be noted for Study B that no statistical adjustment for multiplicity was carried out.

Table 1. Summary of the Soriatane Efficacy Results of the 8-Week Double-Blind Phase of Studies A and B

	Study A		Study B		
	Total daily dose		Total daily dose		
Efficacy Variables	**Placebo (N=29)**	**50 mg (N=29)**	**Placebo (N=72)**	**25 mg (N=74)**	**50 mg (N=71)**
Physician's Global Evaluation					
Baseline Mean	4.62	4.55	4.43	4.37	4.49
Change After 8 Weeks	−0.29	−2.00*	−0.06	−1.06*	−1.57*
Scaling					
Baseline Mean	4.10	3.76	3.97	4.11	4.10
Change After 8 Weeks	−0.22	−1.62*	−0.21	−1.50*	−1.78*
Thickness					
Baseline Mean	4.10	4.10	4.03	4.11	4.20
Change After 8 Weeks	−0.39	−2.10*	−0.18	−1.43*	−2.11*
Erythema					
Baseline Mean	4.21	4.59	4.42	4.24	4.45
Change After 8 Weeks	−0.33	−2.10*	−0.37	−1.12*	−1.65*

*Values were statistically significantly different from placebo and from baseline ($p \leq 0.05$). No adjustment for multiplicity was done for Study B.

The efficacy variables consisted of: the mean severity rating of scale, lesion thickness, erythema, and the physician's global evaluation of the current status of the disease. Ratings of scaling, erythema, and lesion thickness, and the ratings of the global assessments were made using a seven-point scale (0 = none, 1 = trace, 2 = mild, 3 = mild-moderate, 4 = moderate, 5 = moderate-severe, 6 = severe).

A subset of 141 patients from both pivotal studies A and B continued to receive Soriatane in an open fashion for up to 24 weeks. At the end of the treatment period, all efficacy variables, as indicated in Table 2, were significantly improved ($p \leq 0.01$) from baseline, including extent of psoriasis, mean ratings of psoriasis severity and physician's global evaluation.

Table 2. Summary of the First Course of Soriatane Therapy (24 Weeks)

Variables	Study A	Study B
Mean Total Daily Soriatane Dose (mg)	42.8	43.1
Mean Duration of Therapy (Weeks)	21.1	22.6
Physician's Global Evaluation	N = 39	N = 98
Baseline	4.51	4.43
Mean Change From Baseline	−2.26*	−2.60*
Scaling	N = 59	N = 132
Baseline	3.97	4.07
Mean Change From Baseline	−2.15*	−2.42*
Thickness	N = 59	N = 132
Baseline	4.00	4.12
Mean Change From Baseline	−2.44*	−2.66*
Erythema	N = 59	N = 132
Baseline	4.35	4.33
Mean Change From Baseline	−2.31*	−2.29*

*Indicates that the difference from baseline was statistically significant ($p \leq 0.01$).

The efficacy variables consisted of: the mean severity rating of scale, lesion thickness, erythema, and the physician's global evaluation of the current status of the disease. Ratings of scaling, erythema, and lesion thickness, and the ratings of the global assessments were made using a seven-point scale (0 = none, 1 = trace, 2 = mild, 3 = mild-moderate, 4 = moderate, 5 = moderate-severe, 6 = severe).

All efficacy variables improved significantly in a subset of 55 patients from Study A treated for a second, 6-month maintenance course of therapy (for a total of 12 months of treatment); a small subset of patients (n = 4) from Study A continued to improve after a third 6-month course of therapy (for a total of 18 months of treatment).

INDICATIONS AND USAGE

Soriatane is indicated for the treatment of severe psoriasis in adults. Because of significant adverse effects associated with its use, Soriatane should be prescribed only by those knowledgeable in the systemic use of retinoids. In females of reproductive potential, Soriatane should be reserved for non-pregnant patients who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments (see boxed CONTRAINDICATIONS AND WARNINGS — Soriatane can cause severe birth defects).

Most patients experience relapse of psoriasis after discontinuing therapy. Subsequent courses, when clinically indicated, have produced efficacy results similar to the initial course of therapy.

CONTRAINDICATIONS

Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).

Soriatane is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values (see boxed WARNINGS: *Hepatoxicity*, WARNINGS: *Lipids and Possible Cardiovascular Effects*, and PRECAUTIONS).

An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with Soriatane is also contraindicated (see PRECAUTIONS: *Drug Interactions*).

Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see WARNINGS: *Pseudotumor Cerebri*).

Soriatane is contraindicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

WARNINGS

(see also boxed CONTRAINDICATIONS AND WARNINGS)

Hepatotoxicity: **Of the 525 patients treated in US clinical trials, 2 had clinical jaundice with elevated serum bilirubin and transaminases considered related to Soriatane treatment. Liver function test results in these patients returned to normal after Soriatane was discontinued. Two of the 1289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal 2 months after Soriatane was discontinued.**

The potential of Soriatane therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed

Timing of Paternal Acitretin Treatment Relative to Conception	Delivery of Healthy Neonate	Spontaneous Abortion	Induced Abortion	Total
At time of conception	5*	5	1	11
Discontinued ~4 weeks prior	0	0	1**	1
Discontinued ~6 to 8 months prior	0	1	0	1

* Four of 5 cases were prospective.

** With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus).

Continued on next page

Permax—Cont.

Events Observed During the Premarketing Evaluation of Permax — This section reports event frequencies evaluated as of October 1988 for adverse events occurring in a group of approximately 1800 patients who took multiple doses of pergolide. The conditions and duration of exposure to pergolide varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Frequent:* headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System — *Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System — *Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System — *Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System — *Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System — *Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System — *Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System — *Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusions, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System — *Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System — *Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System — *Frequent:* abnormal vision, diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System — *Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

Postintroduction Reports — Voluntary reports of adverse events temporally associated with pergolide that have been received since market introduction and which may have no causal relationship with the drug, include the following: neuroleptic malignant syndrome and Raynaud's phenomenon.

OVERDOSAGE

There is no clinical experience with massive overdosage. The largest overdose involved a young hospitalized adult patient who was not being treated with pergolide but who intentionally took 60 mg of the drug. He experienced vomiting, hypotension, and agitation. Another patient receiving a daily dosage of 7 mg of pergolide unintentionally took 19 mg/day for 3 days, after which his vital signs were normal but he experienced severe hallucinations. Within 36 hours of resumption of the prescribed dosage level, the hallucinations stopped. One patient unintentionally took 14 mg/day for 23 days instead of her prescribed 1.4 mg/day dosage. She experienced severe involuntary movements and tingling in her arms and legs. Another patient who inadvertently received 7 mg instead of the prescribed 0.7 mg experienced palpitations, hypotension, and ventricular extrasystoles. The highest total daily dose (prescribed for several patients with refractory Parkinson's disease) has exceeded 30 mg.

Symptoms — Animal studies indicate that the manifestations of overdosage in man might include nausea, vomiting, convulsions, decreased blood pressure, and CNS stimulation. The oral median lethal doses in mice and rats were 54 and 15 mg/kg respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference* (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Management of overdosage may require supportive measures to maintain arterial blood pressure. Cardiac function should be monitored; an antiarrhythmic agent may be necessary. If signs of CNS stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdose has not been assessed.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

There is no experience with dialysis or hemoperfusion, and these procedures are unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

Administration of Permax should be initiated with a daily dosage of 0.05 mg for the first 2 days. The dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal therapeutic dosage is achieved.

Permax is usually administered in divided doses 3 times per day. During dosage titration, the dosage of concurrent *l*-dopa/carbidopa may be cautiously decreased.

In clinical studies, the mean therapeutic daily dosage of Permax was 3 mg/day. The average concurrent daily dosage of *l*-dopa/carbidopa (expressed as *l*-dopa) was approximately 650 mg/day. The efficacy of Permax at doses above 5 mg/day has not been systematically evaluated. Doses of pergolide above 5 mg/day are not recommended (*see* WARNINGS).

HOW SUPPLIED

Tablets (modified rectangle shape, scored):

0.05 mg, ivory, debossed with A 024, in bottles of 30 (UC5336) — NDC 0187-0839-01

0.25 mg, green, debossed with A 025, in bottles of 100 (UC5337) — NDC 0187-0840-02

1 mg, pink, debossed with A 026, in bottles of 100 (UC5338) — NDC 0187-0841-02

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

PERMAX is a registered trademark of Eli Lilly and Company, and licensed in the US to Valeant Pharmaceuticals North America.

Manufactured for:
Valeant Pharmaceuticals North America
One Enterprise
Aliso Viejo, CA 92656 U.S.A.
Part No. 3083900EX00
Revision: 1-06

TASMAR®

(tolcapone)

TABLETS

℞

Before prescribing TASMAR, the physician should be thoroughly familiar with the details of this prescribing information.

TASMAR SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS AND THE PATIENT HAS PROVIDED WRITTEN ACKNOWLEDGEMENT THAT THE RISKS HAVE BEEN EXPLAINED (SEE PATIENT ACKNOWLEDGEMENT OF RISKS SECTION).

WARNING

Because of the risk of potentially fatal, acute fulminant liver failure, TASMAR (tolcapone) should ordinarily be used in patients with Parkinson's disease on l-dopa/carbidopa who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies (see INDICATIONS and DOSAGE AND ADMINISTRATION sections).

Because of the risk of liver injury and because TASMAR, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn from TASMAR.

TASMAR therapy should not be initiated if the patient exhibits clinical evidence of liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal. Patients with severe dyskinesia or dystonia should be treated with caution (see PRECAUTIONS: *Rhabdomyolysis*).

Patients who develop evidence of hepatocellular injury while on TASMAR and are withdrawn from the drug for any reason may be at increased risk for liver injury if TASMAR is reintroduced. Accordingly, such patients should not ordinarily be considered for retreatment.

Cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in postmarketing use. As of May 2005, 3 cases of fatal fulminant hepatic failure have been reported from more than 40,000 patient years of worldwide use. This incidence may be 10- to 100-fold higher than the background incidence in the general population. Underreporting of cases may lead to significant underestimation of the increased risk associated with the use of TASMAR. All 3 cases were reported within the first six months of initiation of treatment with TASMAR. Analysis of the laboratory monitoring data in over 3,400 TASMAR-treated patients participating in clinical trials indicated that increases in SGPT/ALT or SGOT/AST, when present, generally occurred within the first 6 months of treatment with TASMAR.

A prescriber who elects to use TASMAR in face of the increased risk of liver injury is strongly advised to monitor patients for evidence of emergent liver injury. Patients should be advised of the need for self-monitoring for both the classical signs of liver disease (e.g., clay colored stools, jaundice) and the nonspecific ones (e.g., fatigue, loss of appetite, lethargy).

Although a program of periodic laboratory monitoring for evidence of hepatocellular injury is recommended, it is not clear that periodic monitoring of liver enzymes will prevent the occurrence of fulminant liver failure. However, it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Accordingly, the following liver monitoring program is recommended.

Before starting treatment with TASMAR, the physician should conduct appropriate tests to exclude the presence of liver disease. In patients determined to be appropriate candidates for treatment with TASMAR, serum glutamic-pyruvic transaminase (SGPT/ALT) and serum glutamic-oxaloacetic transaminase (SGOT/AST) levels should be determined at baseline and periodically (i.e. every 2 to 4 weeks) for the first 6 months of therapy. After the first six months, periodic monitoring is recommended at intervals deemed clinically relevant. Although more frequent monitoring increases the chances of early detection, the precise schedule for monitoring is a matter of clinical judgement. If the dose is increased to 200 mg tid (see DOSAGE AND ADMINISTRATION section), liver enzyme monitoring should take place before increasing the dose and then be conducted every 2 to 4 weeks for the following 6 months of therapy. After six months, periodic monitoring is recommended at intervals deemed clinically relevant.

TASMAR should be discontinued if SGPT/ALT or SGOT/AST levels exceed 2 times the upper limit of normal or if clinical signs and symptoms suggest the onset of hepatic dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, and right upper quadrant tenderness).

DESCRIPTION

TASMAR® is available as tablets containing 100 mg or 200 mg tolcapone.

Tolcapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is used in the treatment of Parkinson's disease as

PRODUÇT INFORMATION

3 or more missed pills	• Contact your health care professional for further advice. Keep taking one pill every day until you reach your health care professional. Do not take the missed pills. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED

Use a BACK-UP NONHORMONAL BIRTH-CONTROL METHOD anytime you have sex.

KEEP TAKING ONE PILL EACH DAY until you can reach your health care professional.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately 1-2% per year (1 to 2 pregnancies per 100 women per year of use) if taken every day as directed, but the average failure rate is approximately 5% per year (5 pregnancies per 100 women per year of use) including women who do not always take the pill exactly as directed without missing any pills. If you do become pregnant, the risk to the fetus is minimal, but you should stop taking your pills and discuss the pregnancy with your health care professional.

PREGNANCY AFTER STOPPING THE PILL

If you do not desire pregnancy, you should use another method of birth-control immediately after stopping Lybrel. A pregnancy can occur within days after stopping Lybrel.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

OVERDOSAGE

Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain, and fatigue/drowsiness. Withdrawal bleeding may occur in females. In case of overdosage, contact your health care professional or pharmacist.

OTHER INFORMATION

Your health care professional will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care professional believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health care professional if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care professional, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, some information suggests that the use of oral contraceptives provide certain other benefits. The benefits are:

- Decreased blood loss, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other cycle-related symptoms may occur less frequently.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your health care professional or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

Wyeth®

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

W10522C002
ET02
Rev 05/07

Shown in Product Identification Guide, page 335

MYLOTARG®

℞

(mī'-lō-tärg)

(gemtuzumab ozogamicin for Injection)

FOR INTRAVENOUS USE ONLY

℞ **only**

This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

WARNINGS

Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

There are no controlled trials demonstrating efficacy and safety using Mylotarg in combination with other chemotherapeutic agents. Therefore, Mylotarg should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

Severe myelosuppression occurs when Mylotarg is used at recommended doses.

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS, INFUSION REACTIONS, PULMONARY EVENTS

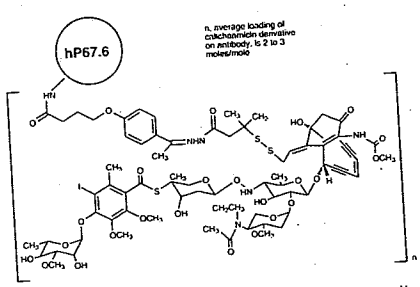
Mylotarg administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of Mylotarg and resolved. Mylotarg infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Mylotarg treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for pulmonary events and tumor lysis syndrome, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/μL prior to administration of Mylotarg. (See **WARNINGS**.)

HEPATOTOXICITY:

Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of Mylotarg as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem cell transplant (HSCT). Patients who receive Mylotarg either before or after HSCT, patients with underlying hepatic disease or abnormal liver function, and patients receiving Mylotarg in combinations with other chemotherapy are at increased risk for developing VOD, including severe VOD. Death from liver failure and from VOD has been reported in patients who received Mylotarg. Physicians should monitor their patients carefully for symptoms of hepatotoxicity, particularly VOD. These symptoms can include: rapid weight gain, right upper quadrant pain, hepatomegaly, ascites, elevations in bilirubin and/or liver enzymes. However, careful monitoring may not identify all patients at risk or prevent the complications of hepatotoxicity. (See **WARNINGS** and **ADVERSE REACTIONS** sections.)

DESCRIPTION

Mylotarg® (gemtuzumab ozogamicin for Injection) is a chemotherapy agent composed of a recombinant humanized IgG4, kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, isolated from fermentation of a bacterium, *Micromonospora echinospora* subsp. *calichensis*. The antibody portion of Mylotarg binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells.



The anti-CD33 hP67.6 antibody is produced by mammalian cell suspension culture using a myeloma NS0 cell line and is purified under conditions which remove or inactivate viruses. Three separate and independent steps in the hP67.6 antibody purification process achieves retrovirus inactivation and removal. These include low pH treatment, DEAE-Sepharose chromatography, and viral filtration. Mylotarg contains amino acid sequences of which approximately 98.3% are of human origin. The constant region and framework regions contain human sequences while the complementarity-determining regions are derived from a murine antibody (p67.6) that binds CD33. This antibody is linked to N-acetyl-gamma calicheamicin via a bifunctional linker. Gemtuzumab ozogamicin has approximately 50% of the antibody loaded with 4–6 moles calicheamicin per mole of antibody. The remaining 50% of the antibody is not linked to the calicheamicin derivative. Gemtuzumab ozogamicin has a molecular weight of 151 to 153 kDa.

Mylotarg is a sterile, white, preservative-free lyophilized powder containing 5 mg of drug conjugate (protein equivalent) in an amber vial. The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. The inactive ingredients are: dextran 40; sucrose; sodium chloride; monobasic and dibasic sodium phosphate.

CLINICAL PHARMACOLOGY

General

Gemtuzumab ozogamicin binds to the CD33 antigen. This antigen is expressed on the surface of leukemic blasts in more than 80% of patients with acute myeloid leukemia (AML). CD33 is also expressed on normal and leukemic myeloid colony-forming cells, including leukemic clonogenic precursors, but it is not expressed on pluripotent hematopoietic stem cells or on nonhematopoietic cells.

Mechanism of Action: Mylotarg is directed against the CD33 antigen expressed by hematopoietic cells. Binding of the anti-CD33 antibody portion of Mylotarg with the CD33 antigen results in the formation of a complex that is internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to DNA in the minor groove resulting in DNA double strand breaks and cell death.

Gemtuzumab ozogamicin is cytotoxic to the CD33 positive HL-60 human leukemia cell line. Gemtuzumab ozogamicin produces significant inhibition of colony formation in cultures of adult leukemic bone marrow cells. The cytotoxic effect on normal myeloid precursors leads to substantial myelosuppression, but this is reversible because pluripotent hematopoietic stem cells are spared. In preclinical animal studies, gemtuzumab ozogamicin demonstrates antitumor effects in the HL-60 human promyelocytic leukemia xenograft tumor in athymic mice.

Human Pharmacokinetics

After administration of the first recommended 9 mg/m² dose of gemtuzumab ozogamicin, given as a 2 hour infusion, the elimination half lives of total and unconjugated calicheamicin were about 41 and 143 hours, respectively. After the second 9 mg/m² dose, the half life of total calicheamicin was increased to about 64 hours and the area under the concentration-time curve (AUC) was about twice that in the first dose period. The AUC for the unconjugated calicheamicin increased 30% after the second dose. Age, gender, body surface area (BSA), and weight did not affect the pharmacokinetics of Mylotarg.

Patients, especially patients previously treated with HSCT, have an underlying risk of VOD. The AUC of total calicheamicin was correlated with additional risk of hepatomegaly and the risk of veno-occlusive disease (VOD). There is no evidence that reducing Mylotarg dose will reduce the underlying risk of VOD. Metabolic studies indicate hydrolytic release of the calicheamicin derivative from gemtuzumab ozogamicin. Many metabolites of this derivative were found after *in vitro* incubation of gemtuzumab ozogamicin in human liver microsomes and cytosol, and HL-60 promyelocytic leukemia cells. Metabolic studies characterizing the possible isozymes involved in the metabolic pathway of Mylotarg have not been performed.

CLINICAL STUDIES

The efficacy and safety of Mylotarg as a single agent has been evaluated in 277 patients in three single arm open label studies in patients with CD33 positive AML in first relapse. The studies included 84, 95, and 98 patients in studies 1 and 2 patients were ≥ 18 years of age with a remission duration of at least 6 months. In study 3, patients ≥ 60 were enrolled and their first remission had to have lasted for at least 3 months. Patients with secondary leukemia or white blood cell (WBC) counts ≥ 30,000/μL were excluded. Some patients were leukoreduced with hydroxyurea or leukapheresis to lower WBC counts below 30,000/μL in order to minimize the risk of tumor lysis syndrome. The treatment course included two 9 mg/m² doses separated by 14 days and a 28-day follow-up after the first dose. Although smaller doses had elicited responses in earlier studies, the 9 mg/m² was chosen because it would be expected to saturate all CD33 sites regardless of leukemic burden. A total of 157 patients were ≥ 60 years of age and older. The primary endpoint of the three clinical studies was the rate of complete remission (CR), which was defined as:

a. leukemic blasts absent from the peripheral blood;
b. ≤ 5% blasts in the bone marrow, as measured by morphology studies;
c. hemoglobin (Hgb) ≥ 9 g/dL, platelets ≥ 100,000/μL, absolute neutrophil count (ANC) ≥ 1500/μL; and

Continued on next

Albutein—Cont.

ment in the bottle. Do not begin administration more than 4 hours after the container has been entered. Discard unused portion.

PRECAUTIONS

ALBUMIN (HUMAN) U.S.P., ALBUTEIN® should be administered with caution to patients with low cardiac reserve.

Rapid infusion may cause vascular overload with resultant pulmonary edema. Patients should be closely monitored for signs of increased venous pressure.

A rapid rise in blood pressure following infusion necessitates careful observation of injured or postoperative patients to detect and treat severed blood vessels that may not have bled at a lower pressure.

Patients with marked dehydration require administration of additional fluids. ALBUTEIN® may be administered with the usual dextrose and saline intravenous solutions. However, solutions containing protein hydrolysates or alcohol must not be infused through the same administration set in conjunction with ALBUTEIN® since these combinations may cause the proteins to precipitate.

Pregnancy Category C: Animal reproduction studies have not been conducted with Albumin (Human). It is also not known whether Albumin (Human) can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Albumin (Human) should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Allergic or pyrogenic reactions are characterized primarily by fever and chills; rash, nausea, vomiting, tachycardia and hypotension have also been reported. Should an adverse reaction occur, slow or stop the infusion for a period of time which may result in the disappearance of the symptoms. If administration has been stopped and the patient requires additional ALBUMIN (HUMAN) U.S.P., ALBUTEIN®, material from a different lot should be used. ALBUTEIN®, particularly if administered rapidly, may result in vascular overload with resultant pulmonary edema.

DOSAGE AND ADMINISTRATION

ALBUTEIN® is administered intravenously. The total dosage will vary with the individual. In adults, an initial infusion of 100 mL is suggested. Additional amounts may be administered as clinically indicated.

In the treatment of the patient in shock with greatly reduced blood volume, ALBUTEIN® may be administered as rapidly as necessary in order to improve the clinical condition and restore normal blood volume. This may be repeated in 15–30 minutes if the initial dose fails to prove adequate. In the patient with a slightly low or normal blood volume, the rate of administration should be 1 mL per minute.

If dilution of Albutein® 25% is clinically desirable, compatible diluents include sterile 0.9% Sodium Chloride solution or sterile 5% Dextrose in Water.[8]

Pediatric Use: The pediatric use of ALBUMIN (HUMAN) U.S.P., ALBUTEIN®, has not been clinically evaluated. The dosage will vary with the clinical state and body weight of the individual. Historically, a dose one-quarter to one-half the adult dose may be administered, or dosage may be calculated on the basis of 0.6 to 1.0 gram per kilogram of body weight (2.4 to 4mL of ALBUTEIN® 25%). For jaundiced infants suffering from hemolytic disease of the newborn the appropriate dose for binding of free serum bilirubin is 1 gram per kilogram of body weight which may be administered during the procedure.[9] The usual rate of administration in children should be one-quarter the adult rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DIRECTIONS FOR USE (50 mL and 100 mL)

When an Administration Set is Used

Flip off plastic cap on top of the vial and expose rubber stopper. Cleanse exposed rubber stopper with suitable germicidal solution, being sure to remove any excess. Observe aseptic technique and prepare sterile intravenous equipment as follows:

1. Close clamp on administration set.
2. With bottle upright, thrust piercing pin straight through stopper center. Do not twist or angle.
3. Immediately invert bottle to automatically establish proper fluid level in drip chamber (half full).
4. Attach infusion set to administration set, open clamp and allow solution to expel air from tubing and needle, then close clamp.
5. Make venipuncture and adjust flow.
6. Discard all administration equipment after use. Discard any unused contents.

When an Administration Set is Not Used

Flip off plastic cap on top of the vial and expose rubber stopper. Cleanse exposed rubber stopper with suitable germicidal solution, being sure to remove any excess. Observe aseptic technique and prepare sterile intravenous equipment as follows:

1. Using aseptic technique, attach filter needle to a sterile disposable plastic syringe.
2. Insert filter needle into ALBUMIN (HUMAN) U.S.P. ALBUTEIN® 25% Solution.
3. Aspirate ALBUMIN (HUMAN) U.S.P. ALBUTEIN® 25% Solution from the vial into the syringe.
4. Remove and discard the filter needle from the syringe.
5. Attach desired size needle to syringe.
6. Discard all administration equipment after use. Discard any unused contents.

HOW SUPPLIED

1. 50 mL vial ALBUMIN (HUMAN) U.S.P., ALBUTEIN® 25% Solution.
2. 100 mL vial ALBUMIN (HUMAN) U.S.P., ALBUTEIN® 25% Solution.

STORAGE:

ALBUTEIN® is stable for three years providing storage temperature does not exceed 30 °C. Protect from freezing.

Rx only

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Shown in Product Identification Guide, page 317

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IRVINGTON, NY 10579

Direct Inquiries to:
(914) 524-6800
http://www.prestigebrands.com

CLEAREYES OTC

DRUG FACTS

Active ingredients	*Purpose*
Glycerin 0.25%	Lubricant
Naphazoline hydrochloride 0.012%	Redness reliever

USES

- relieves redness of the eye due to minor eye irritations
- for use as a protectant against further irritation or dryness of the eye
- for the temporary relief of burning and irritation due to dryness of the eye

WARNINGS

For external use only

Do not use if solution changes color or becomes cloudy

Ask a doctor before use if you have narrow angle glaucoma

When using this product

- to avoid contamination, do not touch tip to any surface
- replace cap after using
- overuse may produce increased redness of the eye
- pupils may become enlarged temporarily

Stop use and ask a doctor if

- you feel eye pain
- you experience changes in vision
- you experience continued redness or irritation of the eye
- the condition worsens or persists for more than 72 hours

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

DIRECTIONS

Instill 1 to 2 drops in the affected eye(s) up to 4 times daily.

Other information

- store at room temperature
- remove contact lenses before using • **Tamper evident.** Do not use if neckband on bottle is broken or missing.

Inactive ingredients benzalkonium chloride, boric acid, edetate disodium, purified water, sodium borate

Questions? **1-877-274-1787 www.clearеyes.com**

Novartis Pharmaceuticals Corporation

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(888) NOW-NOVARTIS [888-669-6682]
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GLEEVEC® ℞

[glē-vĕk]
(imatinib mesylate)
tablets for oral use

HIGHLIGHTS OF PRESCRIBING INFORMATION

The following prescribing information is based on official labeling in effect September, 2007.

These highlights do not include all the information needed to use Gleevec safely and effectively. See full prescribing information for Gleevec.

GLEEVEC ***(imatinib mesylate)*** **tablets for oral use**
Initial U.S. Approval: 2001

- - - - - - - - - - RECENT MAJOR CHANGES - - - - - - - - -

Indications and Usage: Ph+ CML - Pediatrics (1.3), Ph+ ALL (1.4), MDS/MPD (1.5), ASM (1.6), HES/CEL (1.7), DFSP (1.8) 11/2006

Dosage and Administration: Ph+ CML - Pediatrics (2.2), Ph+ ALL (2.3), MDS/MPD (2.4), ASM (2.5), HES/CEL (2.6), DFSP (2.7) 11/2006

Warnings and Precautions: Severe Congestive Heart Failure and Left Ventricular Dysfunction (5.4) 11/2006

- - - - - - - - - - INDICATIONS AND USAGE - - - - - - - - - -

Gleevec is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Follow up is limited to 5 years (1.1)
- Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy (1.2)
- Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival (1.3)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.4)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements (1.5)
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown (1.6)
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR fusion kinase negative or unknown (1.7)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). The effectiveness of Gleevec in GIST is based on objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. (1.9)

- - - - - - - DOSAGE AND ADMINISTRATION - - - - - - -

- Adults with Ph+ CML CP (2.1): 400 mg/day
- Adults with Ph+ CML AP or BC (2.1): 600 mg/day
- Pediatrics with Ph+ CML (2.2): 340 mg/m^2/day or 260 mg/m^2/day
- Adults with Ph+ ALL (2.3): 600 mg/day
- Adults with MDS/MPD (2.4): 400 mg/day
- Adults with ASM (2.5): 100 mg/day or 400 mg/day
- Adults with HES/CEL (2.6): 100 mg/day or 400 mg/day
- Adults with DFSP (2.7): 800 mg/day
- Adults with GIST (2.8): 400 mg/day or 600 mg/day
- Patients with mild to moderate hepatic impairment (2.9): 400 mg/day
- Patients with severe hepatic impairment (2.9): 300 mg/day

All doses of Gleevec should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. Gleevec can be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

- - - - - - - DOSAGE FORMS AND STRENGTHS - - - - - - -

Tablets (scored): 100 mg and 400 mg (3)

- - - - - - - - - - - - CONTRAINDICATIONS - - - - - - - - - - - -

None (4)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)

Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase. Follow-up is limited to 5 years.

1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy

Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

1.3 Pediatric Patients with Ph+ CML in Chronic Phase

Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

1.4 Ph+ Acute Lymphoblastic Leukemia (ALL)

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia

1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements

1.6 Aggressive Systemic Mastocytosis (ASM)

Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown

1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)

Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown

1.8 Dermatofibrosarcoma Protuberans (DFSP)

Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans

1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)

Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. The effectiveness of Gleevec in GIST is based on objective response rate [*see Clinical Studies (14.8)*]. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

2 DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate. The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, Gleevec treatment can be given as a once-daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 2 years of age.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron.

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

2.1 Adult Patients with Ph+ CML CP, AP and BC

The recommended dose of Gleevec is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

2.2 Pediatric Patients with Ph+ CML

The recommended dose of Gleevec for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). The recommended Gleevec dose is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

2.3 Ph+ ALL

The recommended dose of Gleevec is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

2.4 MDS/MPD

The recommended dose of Gleevec is 400 mg/day for adult patients with MDS/MPD.

2.5 ASM

The recommended dose of Gleevec is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Gleevec 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

2.6 HES/CEL

The recommended dose of Gleevec is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

2.7 DFSP

The recommended dose of Gleevec is 800 mg/day for adult patients with DFSP.

2.8 GIST

The recommended dose of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic malignant GIST.

2.9 Dose Modification Guidelines

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored [*see Drug Interactions (7.1)*].

Hepatic Impairment: Patients with mild and moderate hepatic impairment do not require a dose adjustment but should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment [*see Use in Specific Populations (8.6)*].

Continued on next page